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ABSTRACTS OF WORLD MEDICINE

VOL. 32 No. 1

JULY, 1962

Pathology

EXPERIMENTAL PATHOLOGY

1. Absence of Interferon in Lungs from Fatal Cases of Influenza

S. BARON and A. ISAACS. *British Medical Journal [Brit. med. J.]* 1, 18-20, Jan. 6, 1962. 8 refs.

Interferon is an antiviral substance produced by virus-infected cells. A method for the assay of human interferon was devised at the National Institute for Medical Research, London, and applied in the investigation of lung specimens from patients with influenzal pneumonia. Any influenza virus in the specimens was inactivated by dialysing the 10 to 20% tissue extracts to pH2 and returning the material to pH7. Dilutions of the extracts were made in Medium 199 containing 15% skim milk, and 1 ml. of each dilution was added to primary cultures of human thyroid cells and incubated for 24 hours on a roller drum at 36° C. The fluids were decanted and the cell sheets rinsed thrice, and then 1 ml. of a 10⁻⁴ dilution of vaccinia virus was added. After incubation for 2 hours on a roller drum at 36° C. the fluid was removed and 2 ml. of nutrient agar added to form a thin shell overlay. This was composed of Earle's balanced salt solution containing Eagle's nutrients, 0.5% lactalbumin hydrolysate, 15% skim milk, 1:30,000 neutral red, and 1.5% Noble's agar. The tubes were then incubated at 36° C. in a stationary position and the vaccinia plaques counted between the 3rd and 5th days. The titre was expressed as the dilution giving 50% of inhibition of the plaque number. Specimens from 11 fatal cases of influenzal pneumonia from 4 different localities showed no detectable interferon when tested by this method.

The authors also investigated the effect of interferon on the multiplication of human thyroid cells in culture, but failed to demonstrate any difference in the growth rate of treated and untreated cells. J. E. M. Whitehead

2. The Role of Local Cholesterol Reutilization in Atherogenesis

A. LAZZARINI-ROBERTSON JR. *Archives of Surgery [Arch. Surg.]* 84, 41-48, Jan., 1962. 4 figs., 32 refs.

Since no satisfactory correlation between plasma lipid levels and the degree of atherosclerosis, whether observed clinically or produced experimentally, has been established the author has investigated the problem further by means of recently developed organ culture methods. For this purpose the intima of human arteries was isolated and the local factors concerned in the metabolism and transport of lipids and lipoproteins were studied in cell cultures of specimens of the aorta and various systemic arteries removed from (1) patients aged under 30 dying from trauma with no histological evidence of arterial disease; (2) patients of all ages

with severe atherosclerosis; (3) arteries and aortas from patients with gross evidence of arterial disease removed at the time of reconstructive surgery; and finally (4) arterial homografts which had been implanted into human patients, normal dogs, and hypothyroid dogs with blood cholesterol levels of 800 mg. per 100 ml. or higher. In addition to complicated microchemistry, all cultures were regularly checked by contrast and electron microscopy. The organ cultures were studied in respect of two morphologically and functionally different cell types isolated from the intima: those designated Type I, which were flat, polygonal cells containing abundant oxidative and other enzymes; and Type-II cells, which were without these enzymes and were growing in radiating strands resembling the fibroblasts of connective tissue.

The results of these experiments seemed to indicate that intimal cells of Type I possess the characteristics of reticulo-endothelial cells—that is, when challenged with cholesterol they were able to neutralize it locally. Temporary hyperlipaemia, however, such as occurs after ingestion of a high-fat meal, initiated a process which gradually replaced the Type-I cells with spindle-shaped Type-II cells. Local factors, such as fibrin deposition, haemodynamic changes, and anoxia, also contributed to convert these spindle-shaped Type-II cells into a "fibrous plaque" which showed a qualitative inability to metabolize excess protein-bound cholesterol. It is suggested that these "pre-atherosclerotic" changes increase the inability of the arterial intima to handle a temporary metabolic overload (for example, a fatty meal) and the temporary increase of lipoproteins might act as a trigger mechanism to initiate and extend the vascular changes. In the author's opinion this sequence of events could explain the not infrequent clinical finding of patients with severe atherosclerotic lesions in whom nevertheless the serum cholesterol level and the serum lipoprotein pattern are normal.

[This very complicated and most interesting paper must be read in the original by everyone who wishes to follow the author's sometimes ingenuous interpretation of the findings.] Z. A. Leitner

3. Factors Influencing the Segmental Deposition of Atheromatous Material

S. E. STEPHENSON JR., G. V. MANN, R. YOUNGER, and H. W. SCOTT JR. *Archives of Surgery [Arch. Surg.]* 84, 49-55, Jan., 1962. 5 figs., 8 refs.

The aim of this experimental study carried out at Vanderbilt University, Nashville, Tennessee, was to assess the role of "mechanical" factors in the segmental distribution of atherosclerosis. It was performed on 10 groups of mongrel dogs which, after various experimental alterations of the

aorta, were maintained on a well controlled atherogenic dietary regimen. The alterations in the aorta consisted in: (1) the production of periaortic fibrosis by the insertion of powdered asbestos around the vessel; (2) injection of sodium morrhuate into the adventitia; (3) a segment of the lumbar aorta was resected, rotated, reversed, and reinserted with end-to-end suture; and (4) operative creation of coarctation in the descending branch of the thoracic aorta.

Two facts emerged from these experiments. The variation and extent of the atheromatous lesion were in all cases related to intensity and duration of hypercholesterolaemia. The most extensive deposits were observed in animals in which the serum cholesterol values reached and maintained very high levels. The distribution and concentration of the major lesions were influenced, however, by the experimentally induced mechanical alterations in the aorta, focal or segmental concentration of the atheromatous lesion occurring at the site of the trauma. No focal lesions were produced by periadventitial injection of sodium morrhuate, but in the dogs in which periaortic fibrosis was produced and in those subjected to grafting of the aorta the atheroma encircled the aortic lumen. In animals with experimental coarctation the focal concentration of the atheromatous deposition was not confined to the surgical constriction only, but was present also proximal to it. This latter observation supports the clinical concept that hypertension enhances atherogenesis.

It is suggested that the finding of increased atheromatosis at the site of periaortic fibrosis indicates that blockage of the microcirculation diminishes the drainage of lipids from the arterial wall, though it is noted that increased deposition of atheromatous plaques was observed in the aorta proximal to the coarctation, where no such disturbance in the microcirculation existed. On the basis of the lipid transport mechanism this can be explained only by the assumption that hypertension increases the lipid filtration rate from the arterial lumen and reduces its drainage, thus leading to an intramural accumulation of the atheromatous material. Repetitive pulsative stress resulting in tissue injury is increased by hypertension at the site of a trauma and is considered to be an additional mechanical factor in determining the location of atheromatous deposits. *Z. A. Leitner*

4. **Effect of Antibodies against Rat γ -Globulin or Rat Albumin on Isolated Peritoneal Rat Mast Cells**
R. KELLER. *Nature [Nature (Lond.)]* 193, 282-283; Jan. 20, 1962. 2 figs., 4 refs.

It has been shown that anti-rat serum injected intravenously causes anaphylaxis in albino rats and the release of histamine from the isolated peritoneal mast cells. The results of experiments reported from the Federal Institute of Technology, Zürich, showed, in 15 to 25 duplicate estimations on each group, that rabbit whole-rat-serum antiserum produced the release of 36% of the total histamine present in the isolated mast cells, while rabbit rat- γ -globulin antiserum effected the release of 78% of the available histamine. On the other hand rat-albumin antiserum did not release histamine in any significant amount (4%). The histamine release was found to be dependent on temperature, as in other immunological systems involving mast cells.

[Any factual bridge which helps to span the gap between the various hypothetical conceptions of the aetiology of the rheumatoid disease process should prove of value. Possible

relationships may be involved concerning allergic and autoimmune hypotheses and the reported increase in tissue mast cells in rheumatoid arthritis.] *Harry Coke*

CHEMICAL PATHOLOGY

5. **Factors Affecting Lactic Dehydrogenase and Glutamic Oxalacetic Transaminase Activities in Cerebrospinal Fluid**
H. SPOLTER and H. G. THOMPSON JR. *Neurology [Neurology (Minneapolis)]* 12, 53-59, Jan., 1962. 9 figs., 12 refs.

In an investigation at the University of Wisconsin Medical School, Madison, the total protein and gamma-globulin levels and the lactic dehydrogenase (L.D.H.) and glutamic-oxalacetic transaminase (G.O.T.) activities in the cerebrospinal fluid (C.S.F.) have been determined in healthy subjects and in patients suffering from a variety of neurological disorders.

It was confirmed that the C.S.F. protein level increases with age and that a parallel increase in L.D.H. and G.O.T. activity takes place. The relation of L.D.H. and G.O.T. activity to the protein level was frequently disturbed in some neurological conditions. Patients suffering from meningioma and disseminated sclerosis had lower L.D.H. and G.O.T. activities in relation to the protein level than healthy subjects. It is suggested that the expression of L.D.H. and G.O.T. activities in relation to C.S.F. protein levels may prove of diagnostic value. *H. S. Schutta*

6. **Fibrinolytic Activity of Lung Tissue in Renal Failure**
M. MACLEOD, A. L. STALKER, and D. OGSTON. *Lancet [Lancet]* 1, 191-192, Jan. 27, 1962. 7 refs.

The authors, at the University of Aberdeen, have studied fibrinolytic activity in tissue fragments, potassium thiocyanate extracts, and saline homogenates from a series of lungs obtained from patients who died in renal failure and from a control group without renal failure. A defect in the fibrinolytic enzyme system was found in the cases of renal failure. It seemed more probably due to inhibition of activator than to an absolute enzyme deficiency. It is suggested that the defect may be significant in the formation of excessive fibrinous exudate in renal failure. *H. Harris*

7. **Serum Haptoglobin in Liver Disease**
R. WILLIAMS, B. E. SPEYER, and B. H. BILLING. *Gut [Gut]* 2, 297-303, Dec., 1961. 5 figs., 19 refs.

The serum haptoglobin protein levels were determined at the Royal Free Hospital, London, in 115 patients with liver disease of various types. Contrary to what has occasionally been claimed, it was not possible to observe a regular association of high serum haptoglobin levels with extrahepatic obstructive jaundice and of low levels with intrahepatic obstruction. Thus the authors conclude that the determination of the serum haptoglobin protein level has no place in the differential diagnosis of obstructive jaundice.

It was possible to demonstrate, however, a characteristic pattern in infective hepatitis, consisting of an increasing degree of jaundice accompanied by a fall in serum haptoglobin level. This decrease in haptoglobins was not associated with a fall in serum albumin level or increased haemolysis, and for the present the authors cannot explain this interesting phenomenon. *H. Lehmann*

8. Plasma Free Fatty Acid in Liver Disease

A. MORTIAUX and A. M. DAWSON. *Gut* [Gut] 2, 304-309, Dec., 1961. 6 figs., 27 refs.

In a study carried out at the Royal Free Hospital, London, of the plasma free fatty-acid levels in liver disease, this level was determined in 26 patients with alcoholic cirrhosis, 65 with non-alcoholic cirrhosis (12 with the juvenile type), 14 with primary and 4 with secondary-biliary cirrhosis, 9 with extrahepatic biliary obstruction, 5 with haemochromatosis, and 8 with viral hepatitis, and also in 20 healthy control subjects (medical staff or students). The normal mean fasting venous free fatty-acid level was shown to be 0.52 ± 0.14 mEq. per litre.

In 135 out of 146 determinations in the 131 patients the level was found to be above the normal range. There was no difference between patients with the various types of hepatic disorder. It is pointed out that a raised fatty-acid level in the plasma may theoretically be due to increased mobilization of body fat, to diminished utilization of the free fatty acid, or to hydrolysis of esterified fat in the blood stream. The authors consider that in the case of liver disease the first explanation applies. They found that glucose, which inhibits the peripheral release of free fatty acids, caused in their patients a fall of the plasma fatty-acid level to normal. In addition, by the use of labelled fatty acid they demonstrated that there was an increased plasma flow in patients with liver disease.

H. Lehmann

9. Comparative Value of Tests for Urinary Glucose

J. B. O'SULLIVAN, N. KANTOR, and H. L. C. WILKERSON. *Diabetes* [Diabetes] 11, 53-55, Jan.-Feb., 1962. 5 refs.

The authors have evaluated the qualitative and quantitative accuracy of the copper reduction and glucose oxidase methods of testing for urinary glucose, the specific tests studied being Benedict's test and "clinitest" (both copper oxidase methods) and the commercially available "tes-tape", "clinitix", and "uristix" (glucose oxidase methods).

Preliminary laboratory studies on 104 random urine specimens from diabetic and non-diabetic patients showed the mean proportion of glucose present to be 0.55% by adaptation of the Somogyi-Nelson blood sugar method and 0.47% by the specific quantitative glucose oxidase method of Froesch and Renold. The mean for non-glucose reducing substances by the latter method was 0.07%; however, it was found that about 20% of the specimens gave false positive results by the Somogyi-Nelson method, and contained less than 0.1% of glucose. The quantitative glucose oxidase test was therefore used to test 1,000 urine specimens to act as a standard against which the accuracy of the copper reduction and paper enzyme methods could be judged. In evaluating the results, the accepted arbitrary upper limit of normal urinary glucose was considered to be 0.1% and by this criterion the validity of the tests was determined.

The sensitivity of a test expresses the number of true positive urines ($>0.1\%$ glucose) rated positive by the indicated test. The specificity of a test is its ability to identify negative urines correctly (those with $<0.1\%$ glucose). The authors found that with one exception the sensitivities of all the tests were in good agreement, the exception being the "clinitest", which in some 8% of the known positive urine specimens gave a false negative result. Benedict's test was found to have the most favourable figure for sensitivity, although it has disadvantages in procedure. The paper

enzyme tests gave only 2% false negative tests. The copper reduction tests were the most specific, while the difficulty of deciding between a negative and a trace reaction gave the Benedict test a lower specificity rating. The specificity rating of the paper enzyme tests was less satisfactory than their high sensitivity rating, 6 to 21% of negative urines tested giving false positive results.

All the tests evaluated showed some quantitative value, but the paper enzyme tests demonstrated so wide a range of reaction to the amount of glucose present as to limit their value in the control of diabetes. The copper reduction tests were not subject to such wide fluctuations, thus confirming their value in diabetes control.

John Lister

HAEMATOLOGY

10. Determination of Prothrombin Concentration as an Index of Anticoagulant Control

J. C. OWENS, C. A. ARMBRUST JR., W. C. SUTTON, W. R. LIVESAY, and E. L. WAGNER. *American Journal of Cardiology* [Amer. J. Cardiol.] 8, 471-480, Oct., 1961. 6 figs., 35 refs.

This paper from Hermann Hospital and Baylor University College of Medicine, Houston, Texas, presents a comparative assessment of two methods of controlling anticoagulant treatment—namely, estimation of the prothrombin time by the one-stage method of Quick and the determination of prothrombin concentration by the Biggs modification of the Owren-Aas technique. Daily estimations, both procedures being carried out simultaneously, were made on a group of 50 patients receiving anticoagulants for the first time, and estimations at intervals of one to 4 weeks on a group of 280 out-patients undergoing long-term therapy. A total of 2,500 blood samples were collected during an 18-month period, and on 100 of these proconvertin (Factor VII) concentration was determined by the method of Owren and Aas.

The values for prothrombin time correlated poorly with those for prothrombin concentration. In the group starting treatment with anticoagulants the desired prothrombin time (between 2 and $2\frac{1}{2}$ times the control value) was attained in the majority of cases within 48 hours, at a time when only one of the 50 patients was shown to have a prothrombin concentration within the desired range (10 to 24% of normal). By the 5th day the prothrombin concentration had been reduced to less than 24% of normal in approximately half the patients, and in all the patients by the 10th day.

In the group receiving long-term anticoagulant therapy, of those patients whose prothrombin time was in the desired range the prothrombin concentration was greater than 24% of normal in 9% and less than 10% of normal in 21.5%. Similarly, of those patients whose prothrombin concentration was in the desired range the prothrombin time as estimated by Quick's method was less than twice the control value in 63% and greater than $2\frac{1}{2}$ times the control value in 4% of the cases. The estimated proconvertin concentration correlated more closely with the Quick prothrombin time, suggesting that the so-called "hypoprothrombinaemia" of the first few days of anticoagulant treatment is in fact hypoproconvertinaemia, which may occur in association with a normal plasma concentration of prothrombin.

Haemorrhage [the exact incidence of which is not revealed] did not occur when the prothrombin concentration exceeded

10%, except in patients with demonstrable lesions at the site of bleeding or in those who had received excessive doses of heparin. The authors conclude that the prothrombin concentration is a more accurate guide than prothrombin time in controlling treatment with the coumarin type of anticoagulants.

[The remarkable statement that "the prothrombin concentration was deliberately allowed to fall below 10% in a number of the patients under close observation in the hospital in an attempt to determine whether there might be any relationship between the level of prothrombin and the occurrence of hemorrhage" might expose the authors to criticism on ethical grounds.]

Eirian Williams

11. Studies of Platelet Specific Antigens by Means of Hetero-specific Antisera. [In English]

F. GORSTEIN, C. PAN, G. S. SHINOWARA, and P. A. MIESCHER. *Vox sanguinis [Vox Sang. (Basel)]* 6, 669-682, Nov., 1961 [received Feb., 1962]. 6 figs., 12 refs.

The antigenic specificity of platelets has been shown to depend largely on adsorbed fibrinogen; in this study performed at New York University School of Medicine the authors attempted to determine if there are other constituents not present in blood plasma which are antigenetically characteristic for platelets. The effect of anti-platelet sera was estimated by their inhibitory effect on blood coagulation, as measured by the thromboplastin generation test. It was demonstrated that platelet phospholipid is the antigenic platelet constituent which produces this effect; a similar phospholipid was obtained also from the erythrocytes. Platelet protein appears to be the substrate. Fibrinogen, it is agreed, is an antigen associated with platelets, but the effect is different from that of the phospholipid.

M. C. G. Israëls

12. Specificity in Blood Grouping with Plant Lectins and the Application of N-Lectin to Dry Blood Stains

F. R. SYLVIA and P. L. KIRK. *Journal of Forensic Medicine [J. forensic Med.]* 8, 172-181, Oct.-Dec., 1961. 4 figs., 4 refs.

The authors present a quantitative study of the use of plant lectins A₁, A₂, O, H, M, and N in the grouping of both fresh and dried human blood by direct and inhibition techniques respectively. Lectin M was early found to give poor results as compared with standard anti-M sera and was therefore eliminated from the experiment. Each of the other lectins was prepared in varying dilutions and put up against cells of appropriate blood groups and negative control cells, the degree of agglutination being recorded every 5 minutes on a 4-grade scale. Graphs constructed from the results indicated that, apart from lectin A₁, all the lectins under test showed some failure of specificity with time, but specific and non-specific activity could be easily differentiated by this method.

In confirmatory tests 100 samples of human blood were grouped directly, using anti-M and anti-N sera, and then dried upon glass and regrouped at intervals of up to 10 days by the standard inhibition technique, using anti-M serum and N lectin, together with the data on the latter obtained in the initial experiments. Agreement as to genotype was obtained in all but 2 of the 100 cases; in these 2 the lectin revealed the presence of a weak N, undetected by the N antiserum. The genotype frequencies obtained in this series

accord well with those noted by previous workers and it is concluded that the N lectin is a useful and reliable tool for the grouping of dried blood.

Gilbert Forbes

MORBID ANATOMY AND CYTOLOGY

13. Morbid Anatomy and Histochemistry of Poliomyelitis in Children Vaccinated with Salk Vaccine. (К патоморфологии и гистохимии полиомелита у детей, вакцинированных вакциной Солка)

B. A. ERMAN and N. E. MYLNIKOVA. *Архив Патологии [Arch. Patol.]* 23, 11-16, No. 12, 1961. 5 figs., 14 refs.

The authors report the results of post-mortem histological examination of 3 children, aged from 2½ years to 3 years, who died from poliomyelitis and who had been vaccinated 3 or 4 times with Salk vaccine before contracting the disease. Poliomyelitis virus Type 1 was isolated from the tissues in all 3 cases. The location and character of the pathological changes did not differ from those in unvaccinated cases. Dystrophy with loss of the cytoplasmic ribonucleic acid (RNA) was observed in the majority of the nerve cells, while in a minority of the nerve cells a pyknotic degeneration with retention of RNA took place. Since necropsy was not performed in 2 cases until the day following the death and in the 3rd case 2 days after death, the possibility of post-mortem changes affecting the results is noted.

A. Swan

14. Buccal Cell Changes in Patients with Malignant Tumors

H. E. NIEBURGS, B. E. HERMAN, and H. REISMAN. *Laboratory Investigation [Lab. Invest.]* 11, 80-88, Jan., 1962. 12 figs., 11 refs.

Cellular changes in buccal mucosa cells have been described as occurring in patients with iron-deficiency and megaloblastic anaemias and after irradiation of the uterine cervix; significant nuclear changes have also been noted in buccal cells of patients with malignant tumours. Further investigations have now been carried out at Mount Sinai Hospital, New York, to determine the validity and possible significance of such morphological change. For this purpose buccal smears were obtained from 118 subjects, including 51 patients with malignant tumours, 37 patients with benign surgical conditions, 10 patients with metabolic disorders (including 5 with pernicious anaemia), and 20 healthy subjects (including 16 pregnant women). Ages ranged from 4 years to over 81 years. Air-dried specimens were found to be more satisfactory than those which were immediately fixed in 95% alcohol. All smears were stained and examined for the Feulgen reaction.

A large variety of nuclear alterations were found in buccal mucosa not related to malignant neoplasia. Distinct nuclear alterations were observed in addition to these changes in 34 (72%) of 47 patients with malignant tumours at distant sites. These changes consisted in an increase in nuclear size and a discontinuous nuclear membrane. The nuclear material was heterogeneous and contained numerous (usually more than 10) small, round, clear areas (0.5 to 1.0 μ in diameter) which were Feulgen-negative. The areas were well circumscribed and surrounded by increased amounts of Feulgen-positive chromatin. No malignancy-associated changes could be found in 62 of the 64 patients without demonstrable malignant tumours; the other 2 patients were a 67-year-

old man with diabetes and gangrene of the 5th toe and an 84-year-old woman with an x-ray diagnosis of gastric ulcer. Identical cell alterations were also found in areas adjacent to a malignant tumour.

The authors are unable at present to offer a satisfactory explanation as to the aetiology of these distant changes, but suggest they may reflect a systemic involvement of the mitotic formation of cells in malignant neoplasia.

A. W. H. Foxell

15. Duodeno-jejunal Biopsy in the Investigation of Children with Coeliac Disease

A. H. CAMERON, R. ASTLEY, M. HALLOWELL, A. B. RAWSON, C. G. MILLER, J. M. FRENCH, and D. V. HUBBLE. *Quarterly Journal of Medicine [Quart. J. Med.]* 31, 125-140, Jan., 1962. 14 figs., 29 refs.

Examination at the Children's Hospital, Birmingham, of jejunal biopsy specimens from 37 children with coeliac disease who were then taking a normal diet (after a period on a gluten-free diet) showed that the mucosa had a flat surface composed of irregular epithelial cells with a poorly defined brush border. In 9 of these children biopsy examination was repeated after 3 to 12 months on a gluten-free diet, when the mucosa was found to be unchanged in 2, but was considerably improved in the others. In 2 additional children with coeliac disease jejunal biopsy after 4 years on a gluten-free diet showed a normal histological pattern. All these biopsy specimens were compared with similar specimens from a control series of 14 children with intestinal disorders other than coeliac disease. In only one of these latter, a patient with severe giardiasis, did the mucosal appearances resemble those in coeliac disease, and it was considered possible that this patient also had coeliac disease. It is noted that clinical remission was not always accompanied by histological improvement.

The authors conclude that jejunal biopsy is the most reliable single method for diagnosing coeliac disease. In this study it was performed, under radiological control, in most cases with the aid of a Crosby capsule, but in some with the Shiner or Rubin tube. The degree of alteration in the histological pattern was usefully expressed as a numerical index after a section of the biopsy sample was projected on to a lined card at a standard magnification.

A. Wynn Williams

16. Diagnosis of Amoebic Colitis on Routine Biopsies from Rectum and Sigmoid Colon

T. A. McALLISTER. *British Medical Journal [Brit. med. J.]* 1, 362-364, Feb., 10, 1962. 3 figs., 12 refs.

In this investigation, carried out at the Western Infirmary, Glasgow, varying numbers of *Entamoeba histolytica* were observed in or near the mucous surface layer of paraffin sections of the rectum or sigmoid colon obtained by biopsy from 3 adults initially suspected of having ulcerative colitis. Of these patients one was a Nigerian aged 29, another aged 34 had served with the army in India and Burma, but the third, a man of 53, had never travelled outside Scotland; his case was therefore a clinical curiosity, only about 40 such cases having been reported, though the incidence of symptomless carriers is relatively high. Medical treatment for amoebiasis led to an uneventful recovery in all 3 cases.

This study thus emphasizes the value of examining fixed biopsy material in cases of persistent diarrhoea. Recogni-

tion of amoebae is greatly facilitated by use of the periodic-acid-Schiff staining method, by which they are coloured bright red.

A. Wynn Williams

17. Biopsy of the Rectum as an Aid to the Diagnosis of Amyloidosis

P. H. FENTEM, L. A. TURNBERG, and K. G. WORMSLEY. *British Medical Journal [Brit. med. J.]* 1, 364-367, Feb. 10, 1962. 1 fig., 19 refs.

The usefulness of rectal biopsy in the diagnosis of amyloidosis was confirmed in this study reported from Manchester Royal Infirmary. Amyloid was seen in the submucosal arterioles and vessels of 6 patients in which ancillary evidence of amyloidosis was present. In 18 other patients in whom amyloid disease was a theoretical possibility examination of rectal biopsy specimens and other investigations were negative. The specimens were obtained by means of a modified Truelove salt-suction-biopsy instrument and a sigmoidoscope of the "cold-light" or "proximal-light" type, introduced 5 to 15 cm. into the rectum. They were fixed in 10% formalin, and paraffin sections were stained with haematoxylin and eosin and also with methyl violet and Congo red. Polarized light was also used to test for Congo red birefringence.

A. Wynn Williams

18. A Re-evaluation of Bronchiectasis Using Fume Fixation. I. The Broncho-alveolar Structures: a Preliminary Study

W. HENTEL, A. N. LONGFIELD, and J. GORDON. *Diseases of the Chest [Dis. Chest]* 41, 41-45, Jan., 1962. 8 figs., 12 refs.

Using fume fixation-inflation methods along with stereoscopic study of unstained and stained sections the authors, at the Veterans Administration Hospital, Albuquerque, New Mexico, have investigated non-tuberculous bronchiectasis. They describe 2 types of bronchial disease—congenital and pyogenic bronchiectasis. In the first there is gross bronchial dilatation without destructive or degenerative changes in the adjacent parenchyma, the alveoli being relatively normal. In pyogenic bronchiectasis the alveolar ducts are distorted, the alveolar membrane is enlarged, and there are excess deposition of pigment and also inflammatory changes; the ectasia, however, is not spread so diffusely throughout the lungs.

J. B. Wilson

19. Pathogenic Implications of Alveolitis in Pulmonary Emphysema

A. E. ANDERSON JR. and A. G. FORAKER. *Archives of Pathology [Arch. Path.]* 72, 520-534, Nov., 1961. 12 figs., 30 refs.

In a morphologic study [at the Baptist Memorial Hospital, Jacksonville, Florida] of emphysematous lungs, it was found that bronchiolar stenosis and interstitial alveolar lesions were both usually present. The pathogenic implications of this set of circumstances were discussed. Emphysema is felt to be the result of an interplay between mechanical forces and destructive inflammatory changes.

One form of mechanical stress, increased intraluminal pressures, may result from trapping of air behind stenotic bronchioles. Abnormal external tensions may be produced by fibrous contracture. These, in either event, result in overdistention, but not necessarily disruption of tissue. Evidence that normal alveoli will not rupture at physiologic pressures was briefly reviewed. Some additional weakening

factor may be required. Considerable evidence of parenchymal damage was found in our cases of emphysema.

The earliest indication of alveolar damage was in interstitial alveolitis. During this stage of active inflammation, either total dissolution of septa or only incomplete destruction occurred. If alveolar membranes survived the acute insult, they tended to be attenuated or thickened. The elastica was eventually disrupted and the capillary bed obliterated by the destructive and fibrous processes. It was suggested that these alterations, especially those of an acute nature, render alveolar walls more susceptible to the distending and disruptive effects of dynamic forces.—[Authors' summary.]

20. Atherosclerosis of Human Aorta and Its Coronary and Renal Arteries: a Consideration of Some Hemodynamic Factors Which May be Related to the Marked Differences in Atherosclerotic Involvement of the Coronary and Renal Arteries

S. GLAGOV, D. A. ROWLEY, and R. I. KOHUT. *Archives of Pathology [Arch. Path.]* 72, 558-571, Nov., 1961. 9 figs., 46 refs.

The comparative degree of atherosclerosis in the human aorta and its coronary and renal arteries was studied in each of 200 consecutive autopsies. In addition to separate grading of each of the vessels, each aorta was compared directly with its renal and coronary arteries; each coronary tree was compared directly with its corresponding renal arteries.

Renal arteries were both absolutely and relatively free of atherosclerosis even when arising from severely diseased aortas. In no instance was renal artery atherosclerosis greater than associated abdominal aortic atherosclerosis. In contrast, coronary artery atherosclerosis ranged from minimal to severe in vessels arising from both moderately and severely diseased aortas. Relative "sparing" of the coronary arteries was seen in 34% of cases with moderate or severe aortic atherosclerosis. Relative coronary artery "sparing" was more frequent in females than in males and in normotensive than in hypertensive subjects. Under age 50, females showed twice as much relative coronary artery "sparing" as males. The proportion of relative "sparing" was equal for males and females past the age of 50. Some of these discrepancies may be due to peculiarities of blood flow and the resulting differences in wall tension in the coronary and renal arteries. It is suggested that comparative studies of branches of individual arterial trees might reveal important factors in atherogenesis.—[Authors' summary.]

21. Lymph Node Aspiration

M. H. STICH. *American Journal of the Medical Sciences [Amer. J. med. Sci.]* 243, 1-12, Jan., 1962. 15 figs., 4 refs.

Percutaneous needle aspiration of lymph nodes has been performed by the author over 500 times during the past 10 years at the Jewish Hospital of Brooklyn, New York. He now describes his cytological findings to re-emphasize that this is "a simple, rapid, painless, and accurate diagnostic tool".

Smears of the aspiration material of normal lymph nodes, stained with Wright's and Giemsa's stains, show 90% small lymphocytes and 10% large lymphocytes with occasional haematocytoblasts and reticulum cells. In "chronic non-specific lymphadenitis" there is an increase in the proportion

of larger lymphocytes. In chronic lymphatic leukaemia the nuclei of the lymphocytes have a characteristic spotted appearance with fairly sharply demarcated clumps of dark and light chromatin; there is a normal amount of cytoplasm and the cells are not clumped. The lymphosarcoma cell has no cytoplasm and is an immature cell with a finely granular nucleus and one or more nucleoli.

The characteristic finding in the lymph-node aspirate in Hodgkin's disease is an increase in large monocyotoid cells and occasional multinucleated (Dorothy-Reed) cells. In infectious mononucleosis the picture is of chronic non-specific lymphadenitis with scattered abnormal cells seen characteristically in the peripheral blood in this condition. Langhans's giant cells are found in Boeck's sarcoid. Metastatic tumour cells can be recognized easily. In one case the characteristic Donovan bodies of granuloma inguinale were found.

The paper is well illustrated by 15 high-magnification photomicrographs. H. Caplan

IMMUNOPATHOLOGY

22. Demonstration of an Epithelial Antigen in Colon by Means of Fluorescent Antibodies from Children with Ulcerative Colitis

O. BROBERGER and P. PERLMANN. *Journal of Experimental Medicine [J. exp. Med.]* 115, 13-26, Jan. 1, 1962. 19 refs.

Sera from some patients with ulcerative colitis contain an antibody-like material which reacts with constituents of human colon, as shown by complement-fixation and gel-diffusion tests and by the agglutination of erythrocytes or colloidion particles coated with colonic extract. In the study reported in this paper from the Wenner-Gren Institute for Experimental Biology, Stockholm, the authors attempted to locate the antigen responsible for these reactions. Both direct and indirect methods of staining were used, unfixed sections of normal colon being incubated with either a reactive serum that had been conjugated with fluorescent dyes, or with first an unconjugated serum of γ globulin and then with a conjugated rabbit antihuman γ -globulin serum.

With 6 out of 13 sera from children with ulcerative colitis adsorption of the fluorescent label on to colonic tissue was seen. This fluorescent staining was exclusively mucosal and was especially marked in the cytoplasm of the crypt epithelial cells; basement membranes and nuclei were not stained. Although localization of the staining was similar to that of the blood-group substances of the ABO system, inhibition tests suggested that these latter were not the antigens responsible. Sera from patients with systemic lupus erythematosus and the nephrotic syndrome, which as previously shown by Asherson and Broberger (*Brit. med. J.*, 1961, 1, 1429; *Abstr. Wild Med.*, 1961, 30, 270) also often agglutinate erythrocytes coated with colonic extract, were also tested but did not stain colonic tissue. On the other hand, sera from patients with rheumatoid arthritis, which also contain haemagglutinins, showed diffuse staining of mucosa, submucosa, and muscularis.

[These findings should be compared with those of Calabresi *et al.* (*J. clin. Invest.*, 1961, 40, 2126) who, however, showed that in similar tests carried out with alcohol-fixed blood films instead of unfixed sections of colon, the nuclei were stained.] M. C. Berenbaum

Pharmacology and Therapeutics

23. Starvation Treatment. (Лечение голоданием (Предварительное сообщение))

A. N. BAKULEV and R. S. KOLESNIKOVA. *Клиническая Медицина [Klin. Med. (Mosk.)]* 40, 14-21, Feb., 1962. 2 figs., 6 refs.

The authors report the results of starvation treatment in 98 patients suffering from certain diseases associated with metabolic disorders and obesity, namely, disease of the pancreas and biliary tract (70 cases), coronary arterial disease (19), gastric or duodenal ulcer (16), and various other diseases (3 cases). The patients were given no food whatsoever, but were allowed up to 2 litres a day of "Borzhom" mineral water, which is slightly alkaline. Extensive laboratory tests of the blood, excretion, basal metabolism, and cardiac function were carried out during the period of starvation, which lasted from 10 to 15 days, after which the patients were allowed gradually to resume a normal diet. None of the patients suffered any ill effects from the treatment and a number derived considerable benefit from it.

A. Orley

24. Stimulation of Gastric Secretion in Man by a Serotonin Antagonist

R. H. RESNICK, C. F. ADELARDI, and S. J. GRAY. *Gastroenterology [Gastroenterology]* 42, 22-25, Jan., 1962. 5 refs.

The effect on gastric secretion of 1-methyl-D-lysergic acid butanolamide bimalate (UML-491), a potent serotonin antagonist, was studied at the Peter Bent Brigham Hospital, Boston, in 6 patients with proved peptic ulcer. A histamine stimulation test was carried out (0.01 mg. per kg. body weight) and repeated later after two intramuscular injections of 3 mg. of UML-491, one given 30 minutes before the basal collection of gastric juice and the other 30 minutes before the histamine injection. In all 6 patients the acidity and volume of the basal and post-histamine gastric juice were markedly increased. Two patients were then given an intravenous infusion of 5-hydroxytryptophan (a serotonin precursor) in a dosage of 0.66 mg. per kg. body weight in 500 ml. of saline solution before the UML-491 test. In each case there was no increase in the acidity of the basal gastric juice following UML-491 injection, but the potentiation of the histamine effect was not decreased. The possibility that endogenous serotonin may have an inhibitory effect on gastric secretory function is discussed.

M. Lubran

25. Study of Bromindione, a New Anticoagulant

M. M. SINGER, S. FISCH, and A. C. DEGRAFF. *Journal of the American Medical Association [J. Amer. med. Ass.]* 179, 150-152, Jan. 13, 1962. 3 figs., 8 refs.

A clinical trial in 75 patients of a new oral anticoagulant drug, bromindione (*p*-bromophenylindanedione), is described in this paper from the Veterans Administration Hospital, New York. The drug was found to be potent in low dosage; 12 to 18 mg. induced therapeutic "hypoprothrombinaemia" within 28 to 34 hours. The maintenance dose was 2 to 5 mg. daily; once this was established at a therapeutic level withdrawal of the drug was followed by a slow return of the

prothrombin time towards normal, this taking 3 to 10 days. Vitamin K₁ was an effective antidote.

Comparison of bromindione with some other anticoagulants showed that the simple bromination of phenindione had resulted in a compound of much greater potency by weight and with longer duration of action. Side-effects were minimal. In one case a generalized maculopapular petechial dermatitis was attributed to the drug.

A. S. Douglas

26. Clinical Trial of a New Sulphonamide Diuretic (Cyclopenthiiazide). (Klinische Prüfung eines neuen Sulfonamid-diuretikums (Cyclopenthiiazid))

L. DETTLI and P. SPRING. *Deutsche medizinische Wochenschrift [Dtsch. med. Wschr.]* 86, 2327-2332, Dec. 1, 1961. 2 figs., 13 refs.

From the University Medical Clinic, Basle, is reported a clinical trial of the new sulphonamide diuretic cyclopenthiiazide, which has been shown in experimental animals to be 70 times as powerful as chlorothiazide. The subjects of the trial were 113 male and 6 female patients, all suffering from oedema of various origin. In the event only 94 of these patients could be evaluated, since in 17 the oedema disappeared spontaneously and 8 died. Each patient received 0.25 to 2 mg. of the drug in single doses daily or at 2-day intervals. All the patients received the same diet with a moderate salt intake. The results were assessed on urinary volume, loss of weight, and clinical criteria. Successful treatment was judged to have occurred when body weight continued to decline and finally became constant and the signs of water retention disappeared.

Of the first group of 59 patients with oedema due to ischaemic heart disease, decompensated hypertension, or cardiac failure, 9 lost their oedema without the use of diuretics, one died after 2 days, and 2 were so seriously ill that no change in weight could be obtained with any diuretics; of the remaining 47 patients, however, all were treated with cyclopenthiiazide and 44 responded well. In only 6 cases was a result obtained with 0.25 mg. of the drug, the remainder requiring 0.5 to 1 mg. of cyclopenthiiazide daily. In the second group, which consisted of 32 patients with oedema due to chronic pulmonary disease, 5 were too ill to be evaluated and in 6 the oedema disappeared without treatment; of the remaining 21 patients, 14 responded well. One patient resistant to cyclopenthiiazide responded to 20 mg. of hydrochlorothiazide intravenously.

The remaining groups included patients with oedema associated with cirrhosis of the liver, chronic nephropathy, carcinoma, steroid therapy, acute oedema of the lungs, and digitalis intoxication. Diuretic therapy was unsatisfactory in 5 patients with hepatic cirrhosis and found to be not without risk; 2 case histories are described. Of 8 patients with chronic nephropathy, 2 responded to 0.5 mg. of cyclopenthiiazide, one to this dose with the addition of prednisolone, and one to 400 mg. of chlorthalidone. None of the 3 patients with carcinoma responded to the drug, but 3 who had been receiving steroid therapy and 2 with acute oedema of the lungs responded rapidly to 0.5 and 2 mg. respectively

of cyclopenthiiazide daily. The 2 patients with digitalis intoxication showed no response to this drug or to any other diuretic, but 5 with local oedema responded promptly to 0.5 mg. of cyclopenthiiazide daily. The drug was well tolerated, even after one month of continuous treatment, and there were no subjective complaints. Cyclopenthiiazide has no absolute contraindications and was found to be an effective diuretic.

Anne Tothill

27. Clinical Trial of New Oral Diuretic—SKF 8542

R. J. DONNELLY, P. TURNER, and G. S. C. SOWRY *Lancet* [Lancet] 1, 245-247, Feb. 3, 1962. 3 figs., 4 refs.

In this paper from the Edgware General Hospital, Middlesex, a clinical trial is reported of the effects of a new oral diuretic agent, 2:4:7-triamino-6-phenylteridine ("SKF 8542"), in 13 patients with severe fluid retention. The causative conditions were cardiac failure (9 cases) and the nephrotic syndrome, cardiac failure with the nephrotic syndrome secondary to amyloidosis, cirrhosis of the liver, and malignant lymphatic obstruction causing lymphoedema of the legs (one case each).

After an initial control period of 3 to 5 days the patients were given SKF 8542 in a dosage of 100 to 200 mg. daily. Each patient was weighed daily and the fluid intake and urinary output were measured. Treatment was continued until weight loss ceased or manifestations of fluid retention disappeared. In 8 cases SKF 8542 was the sole diuretic agent (with the exception of a single injection of mersalyl in one case); the response was good in 6 and moderate in 2. [In 3 of these, including the 2 with nephrotic syndrome, prednisone or prednisolone was also being given, which may well have been partly responsible for the diuresis.] The remaining 5 patients received chlorothiazide as well as SKF 8542, the response being good in 2 and moderate in 3. Of the 13 patients, 5 had previously shown resistance to other diuretic agents.

An increase in the blood urea level by 12 to 48 mg. per 100 ml. occurred in 7 of the patients, the level returning to normal after cessation of the treatment. In one other patient, who subsequently died, the blood urea level rose to 192 mg. per 100 ml. during treatment and continued to rise afterwards, but this, it is considered, might not have been due directly to the drug. With the exception of an increase in the serum potassium concentration in this patient, there were no disturbances of the serum electrolyte values, which were estimated weekly. (Potassium supplements were given only to the 5 patients also receiving chlorothiazide.) In one instance there was a fall in the total leucocyte count from 14,000 to 6,500 per c.mm. and in another an eosinophilia of 10 to 15% in a total count of 5,000 per c.mm. Postural hypotension was noted in one patient, while 3 complained of drowsiness.

Of 7 further cases briefly described in an addendum, the diuretic response was good in 3, moderate in 3, and poor in one.

J. J. Segall

28. Preliminary Evaluation of Pholcodine, a New Antitussive Agent

C. E. HEFFRON. *Journal of New Drugs* [J. New Drugs] 1, 217-222, Sept.-Oct., 1961 [received Feb., 1962]. 15 refs.

Pholcodine (morpholinethylmorphine) was given to 54 male prisoners at Washington State Penitentiary, Walla Walla, 19 of whom had acute and 35 had chronic cough.

The dosage ranged from 10 to 60 mg. daily in the acute cases and 20 to 160 mg. daily in the chronic. The results were considered to be excellent or good in 15 of the 19 with acute cough and in 27 of the 35 with a chronic cough. Side-effects were negligible. None of the patients (including 7 former drug addicts) showed any withdrawal symptoms when the drug was suddenly discontinued.

V. J. Woolley

29. The Effect of Persantin on Pulmonary Function. (Die Wirkung von Persantin auf die Lungenfunktion)

H. HOMMA. *Wiener klinische Wochenschrift* [Wien. klin. Wschr.] 73, 831-834, Dec. 1, 1961. 3 figs., 11 refs.

The author has investigated the effect of "persantin" on pulmonary function in 25 patients in the thoracic surgery unit of the Regional Hospital, Natters, Tirol, suffering from a variety of disease conditions; their pulmonary function ranged from normal to one of considerable impairment. Spirograms were taken before and 15 minutes after the intravenous administration of 20 mg. of persantin through a cubital vein, and arterial blood samples were withdrawn from the brachial artery on the opposite side through a Cournand needle serving as a self-retaining cannula, the patients being semi-recumbent throughout the test.

A table of the ventilatory function changes after the administration of persantin (a change being considered significant only when the difference was more than 10% of the initial level in the case of respiratory volume and ventilation figures and more than 20% in the case of residual volume) shows that in most cases there was little or no change in vital capacity, forced expiratory volume in one second, residual volume, minute ventilation, and intake of oxygen. The arterial blood oxygen saturation rose after intravenous persantin by a mean of 2.5% in 22 cases, remained the same in 2, and fell by 2% in one. The O₂ tension was increased in 19 cases (by a mean value of 8 mm. Hg), unchanged in 2, and reduced by from 3 to 8 mm. Hg in 4. The combined CO₂ in plasma was practically unchanged, but the CO₂ tension showed a fall from an average value of 44.6 to 41.6 mm. Hg; the change in pH of arterial blood was similar. Thus except for an increase in alveolar ventilation in a moderate proportion of cases, persantin had no significant influence on respiratory volumes and ventilation figures, despite the convincing improvement in O₂ saturation, O₂ and CO₂ tensions, and pH of arterial blood. The author believes that persantin may have its main action on intrapulmonary gaseous exchange by improving (1) the distribution of inhaled tidal air, (2) diffusion, and (3) pulmonary blood flow, but the measurement of these parameters requires special methods and was not attempted. However, he formed the impression that in some, mainly uncomplicated, cases persantin, besides its well-known coronary vasodilator action, had also a definitely favourable effect on pulmonary function which would warrant its use in patients about to undergo thoracic surgery.

Ferdinand Fok

30. Use of Amiphenazole in Respiratory Failure

G. M. LITTLE. *British Medical Journal* [Brit. med. J.] 1, 223-226, Jan. 27, 1962. 2 figs., 10 refs.

The respiratory stimulant amiphenazole was given at King George V Hospital, Godalming, Surrey, to 16 patients suffering from chronic bronchitis and carbon dioxide retention. Of the 10 patients who received 150 mg. of the drug intravenously, 4 obtained an increase in ventilation and a

lowering of arterial CO_2 tension (pCO_2), but in the other 6 there was no significant change, while of 2 patients who received smaller doses intravenously (50 mg. and 100 mg. respectively), the pCO_2 rose in one and was unchanged in one. However, of 4 patients who received amiphenazone by intramuscular injection in doses of 75 to 150 mg., the pCO_2 responded satisfactorily in all.

Because these 16 patients were seriously ill it was not possible to test the effects of various doses and routes of administration. Accordingly, this was investigated in a volunteer bronchitic patient with relatively moderate elevation of pCO_2 (to 54 mm. Hg). Here 150 mg. of amiphenazone given intravenously produced a prompt rise in minute volume (due almost entirely to an increase in tidal volume) from 7.4 to 9.25 litres per minute, which returned to basal level in 1½ hours. Intramuscular and oral administration of 150 mg. of the drug yielded rises in minute volume to 8.25 and 8.0 litres per minute respectively, the peak effect being reached later (at 1 to 1½ hours) and the total duration of effect being somewhat longer. When 75 mg. was given by the same routes in this mild case responses of the same extent and duration were obtained.

In a further study 5 patients who were comatose regained consciousness within 1 to 2 minutes of receiving amiphenazone, before increased ventilation could have achieved a reduction in pCO_2 , and it seems likely that this effect was due to cerebral stimulation. The improvement in the behaviour of these patients often led to easier nursing management. Some patients suffered transitory vomiting and noticed burning sensations in the skin, especially of the face, but these side-effects were less intense than those observed to follow nikethamide. The author concludes that amiphenazone appears to be an efficient and comparatively non-toxic respiratory stimulant.

[The ventilation rates quoted above were derived by the abstractor from the ventilation curves shown in the author's Figures 1 and 2, since no actual rates are given in the text.]

Bernard J. Freedman

31. Clinical Evaluation of the Effectiveness and Safety of a New Analgesic

O. BRANDMAN. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 242, 694-701, Dec., 1961. 5 refs.

At St. Michael's Hospital, Newark, New Jersey, the new analgesic Ro 4-1778 was first studied in 51 patients suffering from acute pain and 50 from chronic pain of varied aetiology; all the patients had previously been receiving a variety of analgesic drugs, but these were discontinued at the beginning of the present trial. Ro 4-1778 was administered orally in doses of 30 to 60 mg. up to 6 times in 24 hours as required, the duration of treatment ranging from 3 to 12 days in the patients with acute pain and from 2 to 6 weeks in those with chronic pain. The new drug was considered to produce effective analgesia in both groups of patients and side-effects were minimal.

A tolerance study after prolonged administration was also carried out. In this, 50 chronically ill patients received 30 mg. of Ro 4-1778 orally four times a day for one week, followed by 60 mg. four times daily for 3 weeks; then after a medication-free period of 2 weeks the patients were given 60 mg. four times a day for a further 20 weeks. Blood and urine analysis and determination of serum transaminase levels revealed no significant changes and there were no alterations

in serum levels of protein-bound iodine, cholesterol, or sugar, or in the electrocardiogram and electroencephalogram.

Side-effects were minimal and the drug was not found to be addictive.

Mark Swerdlow

32. Potentiation of Morphine Analgesia by Mecamylamine. [In English]

G. P. GUPTA and B. N. DHAWAN. *Archives internationales de pharmacodynamie et de therapie* [Arch. int. Pharmacodyn.] 134, 54-60, Nov. 1, 1961. 3 figs., 17 refs.

The effect of mecamylamine hydrochloride, chlorisondamine chloride ("ecolid"), and pempidine hydrochloride on morphine analgesia was studied at K. G. Medical College, Lucknow, India. The hot-plate method was used for testing analgesia, the temperature of the hot plate being kept at 56.5° C. Two groups each of 20 albino rats received subcutaneous injections of 15 mg. of morphine tartrate per kg. body weight, one of the groups also receiving 10 mg. of mecamylamine per kg. 2 hours before the morphine. In other experiments rats received ecolid and pempidine hydrochloride simultaneously with morphine. Testing was continued half-hourly until in 95% of the animals given a particular hypotensive drug there was no evidence of analgesia.

No analgesic activity was shown by ecolid, mecamylamine, or pempidine when tested alone. There was marked potentiation of morphine analgesia by mecamylamine at all doses of the latter (1, 5, and 10 mg. per kg.). The dose of morphine producing analgesia in 50% of the animals (ED_{50}) was 17.24 mg. per kg.; when morphine was combined with 10, 5, or 1 mg. of mecamylamine per kg. the ED_{50} was 9.49; 10.54, and 11.3 mg. per kg. respectively. After rats had received 10 mg. of mecamylamine per kg. combined with 15 mg. of morphine per kg. there was 35% analgesia after 3 hours, whereas with morphine alone there was only 10% analgesia at the end of 2 hours. Ecolid in a dosage of 5 mg. per kg. produced significant antagonism, but pempidine was without effect.

Anne Tothill

33. A Clinical Study and Comparison of Analgesic Drugs Alvodine, Win 14,265-2 and Win 14,465-2 with Meperidine

A. M. BETCHER, CHIU YUM-SAN, A. N. GODHOLM, and J. ALTER. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 39-45, Jan.-Feb., 1962. 2 figs., 13 refs.

This comparative study of analgesic drugs was carried out at the Hospital for Joint Diseases, New York, on 916 patients during the immediate postoperative period. The patients were divided at random into four groups and given, in rotational order and under "double-blind" conditions, one of the following medications: (1) WIN 14,265-2 in a concentration of 3 mg. per ml.; (2) WIN 14,465-2, 0.1 mg. per ml.; (3) piminodine ("alvodine"), 10 mg. per ml.; or (4) pethidine, 100 mg. per ml. It was found that 20 mg. of piminodine gave satisfactory analgesia in a greater proportion of patients than did 100 mg. of pethidine, and also caused a lower incidence of side-effects. WIN 14,265-2 produced inadequate relief of pain, while with WIN 14,465-2 the results were similar to those of pethidine, but the relief was of shorter duration. Of the 916 patients, 31% did not require any postoperative medication for relief of pain.

Mark Swerdlow

Chemotherapy

34. Antistaphylococcal Activity of Penicillin P-12 (5-Methyl-3-phenyl-4-isoxazolyl Penicillin)

A. C. WHITE and J. SMITH. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 202-208, Feb., 1962. 5 figs., 7 refs.

The activity of a new penicillin, 5-methyl-3-phenyl-4-isoxazolyl penicillin (P-12), which is given by mouth and is resistant to staphylococcal penicillinase, was studied at the University of Louisville School of Medicine, Kentucky. A comparison of its activity *in vitro* with that of benzylpenicillin, phenethicillin, and methicillin showed that P-12 inhibited the growth of large inocula of penicillinase-producing staphylococci at lower concentrations than the other penicillins. Although P-12 was less active on a weight basis than phenethicillin or benzylpenicillin against staphylococci which do not produce penicillinase, it was more active against these bacteria than methicillin. Whereas an increase in the inoculum of penicillinase-producing staphylococci caused a marked increase in the concentration of benzylpenicillin required to inhibit these organisms, very little difference was noted with P-12 and methicillin.

A group of 13 patients who were nasal carriers of coagulase-positive staphylococci were given P-12 in a dosage of 500 mg. every 4 hours. Of these 12 patients, 6 were carriers of staphylococci which produced penicillinase and were resistant to 50 µg. per ml. of benzylpenicillin; the remaining patients were carriers of strains sensitive to 0.2 µg. per ml. or less of benzylpenicillin. All staphylococci were susceptible to 1.56 µg. per ml. of P-12. The carrier rate fell from 100% before treatment to 30% by the 7th day of therapy. In patients who continued to be carriers the number of colonies was reduced. There was no difference in the response between carriers of penicillinase-producing staphylococci and carriers of staphylococci which did not produce penicillinase. The response to P-12 was favourable in 10 patients who had previously been treated with other antibiotics for staphylococcal infections in which many of the staphylococci had proved resistant to benzylpenicillin *in vitro*.

No toxic reactions were encountered in this small group of patients or in the nasal carriers. R. F. Jennison

35. Cancer Chemotherapy by Intra-arterial Infusion: a Preliminary Report Concerning Tumours of the Head and Neck

H. J. ESPINER, K. D. J. VOWLES, and R. M. WALKER. *Lancet* [Lancet] 1, 177-181, Jan. 27, 1962. 1 fig., 4 refs.

Chemotherapy has played little part in the treatment of localized malignant disease, since the doses required cause bone-marrow depression. Regional chemotherapy, however, by means of continuous arterial infusion, allows the drug to be given over a long period with the maximum concentration in the tumour area. This method is particularly applicable to tumours of the head and neck, since this region is supplied by a single main artery on each side. The antimetabolite methotrexate ("amethopterin") has a

greater effect given in this way compared with the same dose given by a single injection, while the greater toxicity which results can be overcome by giving the specific metabolite, folinic acid, intramuscularly.

Since May, 1960, 50 patients with advanced cancer of the head and neck, liver, pelvis, and lower limbs have been treated by this method at Bristol Royal Hospital and the results in 27 with cancer of the head and neck are here presented. The authors' method is as follows. A "portex" nylon intravenous cannula (F.G. 3 or 4) is introduced into the external carotid artery via the superficial temporal or superior thyroid artery, the tip being so placed in the external carotid artery that the flow of the infusate will be maximum in the branches supplying the tumour. Accuracy is essential and can be checked in the darkened theatre by injecting fluorescein (5% in 0.5% sodium bicarbonate) and observing under ultraviolet light the resulting fluorescence, which defines the distribution. The infusion is maintained by gravity for an average period of 3 weeks, but on occasion this has been prolonged to 7 weeks. The dosage of methotrexate is 50 mg. in 24 hours in one litre of saline solution; 5,000 i.u. of heparin is added to the solution and 6 mg. of folinic acid given intramuscularly three times a day. This is continued until oral toxicity (manifested by ulcers) or a fall in the leucocyte count below 3,000 per c.mm. occurs, usually in 5 or 6 days, when 250 to 300 mg. of the drug has been given. The infusion is then maintained with heparin in saline alone until toxic signs abate, when a further course is given. A total dose of 750 mg. in 3 such courses has been given. Since the drug is excreted through the kidneys impaired renal function is a contraindication to such high dosage. After the infusion oral chemotherapy with "cytoxan" is started as soon as the leucocyte count returns to normal, 100 to 150 mg. being given daily to keep the leucocyte count under 5,000 per c.mm.

Of 14 patients with recurrent growth after previous radiotherapy, 7 of whom had also undergone radical surgery, total regression of the tumour was obtained in 2 and partial regression in 4, while of 13 patients who had not received previous radiotherapy, tumour regression was total in 2 and partial in 8. Thus total regression was obtained in 4 cases, in 2 by means of chemotherapy alone. Of these 2 patients, one was a man aged 78 with carcinoma of the cheek involving bone and a fixed metastatic node (duration 13 months), while the other was a man aged 74 with carcinoma of the palate (duration 5 months). In addition in 12 patients there was significant objective improvement for two months or longer. I. G. Williams

36. The Role of 5-Fluorouracil in Malignant Disease

B. J. KENNEDY and A. THEOLOGIDES. *Annals of Internal Medicine* [Ann. Intern. Med.] 55, 719-730, Nov., 1961. 6 figs., 44 refs.

The role of 5-fluorouracil in the treatment of malignant disease has been investigated at the University of Minnesota Medical Center, Minneapolis, the drug being administered

to 118 patients with advanced malignant disease of varied types. These were: carcinoma of breast (43), colon (12), ovary (8), stomach (7), kidney (7), lung (2), and bladder (2); advanced lymphoma (7), melanoma (4), neuroblastoma (4), myeloid leukaemia (2), and sarcoma (6); metastatic carcinoma with unknown primary (5); carcinoma of uterus, parotid gland, cervix, testis, adrenal cortex, nasopharynx, gall-bladder, and pancreas (1 each); and carcinoid (1). All patients had active, progressive cancer, the lesions being measurable by clinical, laboratory, and x-ray methods. Response was based on objective criteria only. All patients were admitted to hospital for 2 to 4 weeks for the initial course of therapy; subsequently monthly courses were given in the clinic whenever possible. The drug was injected intravenously in a daily dosage of 15 mg. per kg. body weight for 5 days and then 7.5 mg. per kg. every 2 days until evidence of toxicity appeared. Dosage never exceeded 1 g. daily. Patients who had had previous x-ray therapy or alkylating agents or with extensive tumour involvement of the bone marrow were given a reduced dosage, and if this was tolerated the dose was increased until mild toxicity occurred.

Occasionally a feeling of warmth and a metallic taste were noted during injection, but there was no serious local irritation where there was accidental infiltration into the subcutaneous tissues. During and shortly after the course of injections anorexia, nausea, and occasionally vomiting occurred in 47 of the 77 patients evaluated. A few patients had pain in the tumour mass shortly after injection. Stomatitis occurring on the 3rd to 5th day was one of the earliest signs of toxicity, 75 of 104 patients being thus affected. After 5 to 10 days there was ulceration of the lip and mouth associated with difficulty in swallowing. Severe stomatitis cleared within 2 weeks. Diarrhoea and abdominal cramps in 48 of 73 patients followed the stomatitis; this was controlled with paregoric. Paralytic ileus lasting 10 days occurred in one patient. Examination of the faeces showed shreds of sloughed mucosal tissue; the change in the mucous membrane was characteristic throughout the alimentary tract. Nine out of 69 patients had diffuse erythema, scaling desquamation, or bullous formation followed by hyperpigmentation of the skin; nails were brittle and formed irregular ridges. Alopecia of varying intensity occurred in 48 of 88 patients, but hair grew again even in patients who had repeated courses of therapy. Haematopoietic depression was reflected in the peripheral blood in the form of leucopenia, thrombocytopenia, and mild anaemia. Fever, which appeared to be a general toxic phenomenon and did not respond to intensive broad-spectrum antibiotics, occurred near the end of the 2nd week together with leucopenia and gastro-intestinal symptoms. Toxic reactions were more severe in debilitated patients and those who had had previous intensive irradiation or other cytotoxic chemical therapy.

Of the 118 patients, 107 are dead. There were 7 deaths directly attributable to the treatment, 3 of these being due to profound shock and diarrhoea in debilitated patients. Two patients had massive liver metastases and 3 died of infection, these deaths occurring during the period of maximum leucopenia.

Definite objective improvement of varying duration occurred in 31 of the 118 patients. Of the 43 patients with breast cancer, 18 improved, the improvement in 9 lasting more than 6 months; 7 are still alive. Improvement lasting

6 months was noted in one of the 12 patients with colonic neoplasm and one of the 8 patients with ovarian tumour. Of 7 patients with carcinoma of the stomach, 3 had disappearance of large masses during the toxic reaction of the drug, but these reappeared later. During improvement due to 5-fluorouracil therapy there was a decrease to normal in the hypercalcaemia caused by bone metastases. Measurement of circulating tumour cells in peripheral blood showed a disappearance of neoplastic cells, even though no objective improvement was observed.

The authors conclude that 5-fluorouracil has anti-neoplastic properties which appear to be associated with the severe toxic reaction which this drug evokes. Its most effective application seems to be in the treatment of advanced cancer of the breast.

Anne Tothill

37. An Evaluation of 5-Fluorouracil in Malignant Diseases
A. J. WEISS, L. G. JACKSON, and R. CARABASI. *Annals of Internal Medicine* [Ann. intern. Med.] 55, 731-741, Nov., 1961. 4 figs., 33 refs.

An evaluation of 5-fluorouracil in the treatment of malignant disease is reported from Jefferson Medical College, Philadelphia, Pennsylvania. Included in the study were 144 patients who had obviously incurable carcinoma, patients with leucopenia, thrombocytopenia, or significantly hypoplastic bone marrow being excluded. Patients received 15 mg. of the drug per kg. daily for 5 days; then after an interval of 3 or 4 days 7.5 to 10 mg. per kg. on alternate days until the first signs of toxicity appeared.

Stomatitis was the commonest initial sign of toxicity, generally in patients who received large doses in a short time; diarrhoea, which occurred in those given small doses over a longer period, was also considered an indication for discontinuing treatment. If therapy was not stopped at the first evidence of toxicity, gastro-intestinal and haematological signs were liable to be severe, and usually within 4 days of the appearance of gastro-intestinal toxicity there was evidence of depression of bone-marrow function. Scaling of the skin was not uncommon. Optic neuritis occurred twice in one patient. Seven patients died, probably as a direct result of the treatment.

Of 37 patients with tumours of the colon, 3 had a remission lasting longer than 13 weeks. The symptoms commonly relieved in these cases included intestinal obstruction, bleeding, and deep abdominal pain. The best response was obtained in carcinoma of the breast; of the 38 patients with this form of the disease, 7 had a remission lasting longer than 13 weeks and 15 had an objective response. 5-Fluorouracil was effective in 3 patients with cancer of the breast that had proved refractory to alkylating agents and in 2 whose lesion was refractory to radiotherapy; it was also found to be effective in some patients who were resistant to hormonal therapy. Of 4 patients with an ovarian tumour, one had remission for longer than 13 weeks; and one out of 10 patients treated for gastric tumour had remission for more than 3 months.

The symptoms commonly relieved by 5-fluorouracil therapy include pain, intestinal obstruction, dyspnoea, and dysphagia. Toxicity, however, may be severe, but the drug has a definite though limited value in the treatment of certain malignant conditions, particularly adenocarcinoma of the gastro-intestinal tract and the breast.

Anne Tothill

Infectious Diseases

38. Endemic Influenza. I. Serologic Evidence of Continuing and Subclinical Infection in Disparate Populations in the Post-pandemic Period

J. HAYSLETT, J. MCCARROLL, E. BRADY, K. DEUSCHLE, W. McDERMOTT, and E. D. KILBOURNE. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 1-8, Jan., 1962. 2 figs., 11 refs.

The authors report the results of serological investigations of the occurrence of A2 (Asian) influenza infection in two groups of subjects: (1) an unselected group of 77 Navajo school-children aged from 7 to 15 years living in a reservation in Arizona, and (2) a group of 82 medical students in New York City. All serum specimens were stored and frozen at -30°C . The level of influenza antibody was measured both by the haemagglutination-inhibition technique with an inhibitor-sensitive A2 strain and by a strain-specific complement fixation test, a high-titre strain of A2 virus (Japan 305) being used in the preparation of viral antigen.

The investigation provided evidence of the occurrence of influenza A2 during every year since the pandemic of 1957 in both groups of subjects, despite the absence of recognized community epidemics. The finding in some of the subjects of two separate increases in serum influenza antibody level indicated that there had been more than one infection. Among the Navajo, the only children in whom a significant rise in antibody level was not found were those who had had high levels of antibody at the time of the first test. In both groups of subjects clinical influenza or severe respiratory disease was less common in each post-pandemic year, although there was a slight increase in the incidence of serologically proved infections in the last period in which observations were made (March, 1960). The authors suggest that as population immunity increases, an increasing proportion of influenza infections is becoming clinically inapparent, and conclude that the present results support the view that man is the reservoir of the inter-epidemic influenza virus.

R. G. Meyer

39. Endemic Influenza. II. The Nature of the Disease in the Post-pandemic Period

D. KAYE, M. ROSENBLUTH, E. W. HOOK, and E. D. KILBOURNE. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 9-21, Jan., 1962. 8 figs., 11 refs.

In the first of these two papers [see Abstract 38] it was shown that continuing infection with influenza virus has occurred in the wake of the 1957 pandemic, and this notably in the absence of epidemic disease in the community. The nature of the disease in the post-pandemic period has been investigated by the present authors by means of serological and bacteriological studies on a series of 20 (out of 49) patients admitted to New York Hospital-Cornell Medical Center, New York, between January 18 and April 2, 1960, with an illness suggestive of influenza or showing radiological signs of pulmonary infiltration. It was confirmed by virus isolation, antibody studies, or both, that these 20 patients had influenza due to the A2 (Asian) virus. Of the

13 female patients in the series, 10 were nurses or others connected with the hospital.

The investigation showed that in 12 cases the disease was typical influenza and was free from complications, the majority of these 12 patients being young hospital employees without any chronic disease. In the remaining 8 patients the illness was more severe and was complicated by pulmonary infiltration; of these, 6 were over 40 years of age or had pre-existing disease of the cardiovascular system, and 3 of them developed moderately severe influenzal pneumonia which was classified as "mild segmental influenza virus pneumonia". The results of the investigation give additional support to the view that influenza continues to occur in endemic form in the post-pandemic period and is due to virus of unaltered virulence.

R. G. Meyer

40. Acute Respiratory Disease Associated with Coxsackie A-21 Virus Infection. I. Incidence in Military Personnel: Observations in a Recruit Population

K. M. JOHNSON, H. H. BLOOM, M. A. MUFSON, and R. M. CHANOCK. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 112-119, Jan. 13, 1962. 1 fig., 15 refs.

During the course of an investigation into acute respiratory disease in a military population Coxsackie A21 virus (identical with Coe virus) was recovered from oropharyngeal specimens obtained from 214 of the men, all of whom were new recruits. Anal swab specimens were positive in only about 10% of these patients. During the first 6 weeks of the investigation, which took place at the National Institutes of Health, Bethesda, Maryland, there was a significant association between the isolation of the virus and the incidence of minor respiratory symptoms. During the last 4 weeks of the period there was no such correlation. Virus persisted in the pharynx for as long as 14 days in the natural infections and for as long as 16 to 40 days in 5 inoculated volunteers. Virus-neutralizing antibodies and haemagglutination-inhibiting antibodies were present in only 5 to 10% of the recruits on entry. These antibodies increased in incidence after the infection and were present in 75 to 85% of the population when the outbreak ended.

Winston Turner

41. Acute Respiratory Disease Associated with Coxsackie A-21 Virus Infection. II. Incidence in Military Personnel: Observations in a Nonrecruit Population

H. H. BLOOM, M. M. JOHNSON, M. A. MUFSON, and R. M. CHANOCK. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 120-125, Jan. 13, 1962. 2 figs., 16 refs.

In a "non-recruit" military population Coxsackie A21 virus was recovered from pharyngeal swabs of 39 men. From 122 patients with upper respiratory illness there were 32 virus isolations (26%) compared with 6 virus isolations from 108 men (6%) without such symptoms. The respiratory symptoms were similar to the "common cold syndrome" with slight pyrexia, but there was no clinical difference between the virus-positive and virus-negative patients. Only

3 rectal swab specimens were positive, suggesting a respiratory mode of spread. Antibody estimations revealed that less than 50% of the men in the camp had developed the specific neutralizing antibody at the end of the outbreak of infection. Certain environmental and local climatic conditions, such as temperature and humidity, were considered as possible factors influencing the epidemic.

Winston Turner

42. Hormonal Therapy in Botkin's Disease [Infective Hepatitis]. (Гормональная терапия при болезни Боткина) M. E. SEMENDIAEVA and O. N. MUHINA. *Советская Медицина [Sovetsk. Med.]* 25, 21-31, Jan., 1962. 5 figs., 10 refs.

As there is no specific therapy for Botkin's disease (infective hepatitis) the authors have tried hormonal preparations such as prednisolone, prednisone, and cortisone in the treatment of 107 patients, of whom 68 had acute hepatitis, 15 chronic disease (including cirrhosis of the liver), and 24 obstructive jaundice. Most of the patients were females aged between 21 and 50. The dosage of cortisone was 100 to 200 mg. on the first day, then 50 mg. once or twice a day to a maximum dose of 2,300 mg.; that of prednisone and prednisolone was 15 to 40 mg. daily to a maximum total of 1,170 mg. The duration of treatment ranged from 10 to 49 days.

In 60 patients good results were obtained after 3 to 5 days, these all showing improvement of appetite, less indigestion, less skin irritation, fewer headaches, and absence of malaise. The jaundice diminished very quickly and, especially in the more severe cases, improved considerably during the first weeks of treatment. The authors stress that it is most important to supervise the condition of the patients closely during hormonal treatment; thus blood pressure, serum bilirubin level, transaminase activity, prothrombin index, and blood sugar level should be frequently checked. In their opinion hormonal treatment should not be instituted immediately, but only after other methods of treatment have been tried. They suggest the following indications for hormonal treatment. In acute cases: (1) severe, prolonged acute disease with signs of intoxication following failure of other forms of treatment; (2) cholangiolitic hepatitis; (3) the presence of bilirubinaemia; and (4) hepatic coma, for which steroids are the treatment of choice. In chronic cases the treatment may be of value when there is cirrhosis of the liver with portal hypertension or chronic cholangiolitis. The contraindications are: (1) atrophic cirrhosis of the liver with dilatation of the oesophageal veins; (2) gastric ulcer; and (3) low blood potassium level and a very low prothrombin index. Generally speaking, cases for hormonal treatment should be selected on the individual features which each presents.

H. W. Swann

43. Cat-scratch Disease: Complement Fixation and Skin Test Results

S. S. KALTER. *Annals of Internal Medicine [Ann. Intern. Med.]* 55, 903-910, Dec., 1961. 12 refs.

The results of skin tests were correlated with those of a complement fixation test in patients with cat-scratch disease and in controls. Antigens for the skin test were prepared from human suppurative material. The complement fixation test assessed the antibody response against psittacosis-lymphogranuloma venereum group antigen in acute and

convalescent serum. A positive response, to the complement fixation test was obtained in 26% of 130 patients giving a positive reaction to skin tests, the antibody titre usually being a stationary one and only showing evidence of a four-fold rise in 6 instances. This figure was nevertheless higher than that observed in a control group of 200 patients, 6 of whom showed a stationary antibody titre but none showed a rising titre.

D. Geraint James

44. Psittacosis in Japan: Clinical Observations of 42 Serologically Diagnosed Human Cases

T. GOTO, H. SHIODA, H. NAKAMURA, H. NAITO, S. MATSUHISHIMA, J. MURANO, K. SHIMANO, and M. MATUMOTO. *Japanese Journal of Experimental Medicine [Jap. J. exp. Med.]* 31, 249-258, Aug., 1961 [received March, 1962]. 4 figs., 22 refs.

At the Sagami-hara National Hospital, Kanagawa Prefecture, Japan, complement fixation and haemagglutination inhibition tests were carried out in 599 cases of acute infection of the respiratory tract (including 317 control cases). The antigen used was prepared from allantoic fluid of embryonated eggs infected with the Budgerigar No. 1 strain of psittacosis virus. Evidence of recent psittacosis infection was found in 33 out of 160 patients with primary atypical pneumonia, 7 out of 119 with acute bronchitis, and 2 out of 3 with a middle-lobe syndrome.

The clinical data showed that the viral infection had produced relatively mild symptoms; there were no complications or fatalities. Illness of sudden onset had occurred in 27 cases, the predominant symptoms being fever, cough, expectoration, general malaise, headache, chills, chest pain, and sore throat. No rash was detected. In approximately 50% of the cases the pyrexia subsided within 9 days. In spite of the febrile reaction the pulse rate was relatively slow. Although leucocytosis was not a prominent feature, there was an increased erythrocyte sedimentation rate in almost all cases. Physical signs in the chest were observed towards the end of the first week, but were seldom sharply defined. Radiologically, evidence of pneumonitis was more often encountered on the right side than the left, especially in the lower part of the lung.

Streptomycin and the sulphonamides were found to be of little value in treatment. On the other hand penicillin, chloramphenicol, and tetracycline therapy appeared to exert a beneficial effect. In 12 cases there was spontaneous recovery without chemotherapy.

A. Garland

45. Bacteroides Septicemia: Cultural, Clinical, and Therapeutic Features in a Series of Twenty-five Patients

B. S. TYNES and W. B. FROMMEYER JR. *Annals of Internal Medicine [Ann. intern. Med.]* 56, 12-26, Jan., 1962. 35 refs.

The authors report 25 cases of *Bacteroides* septicemia treated at the University of Alabama Medical Center, Birmingham, in the 6 years 1953-9. In 3 of the cases the organism isolated on blood culture was classified as *B. funduliformis* and in 3 as *B. fragilis*, but in the remaining 19 the species of *Bacteroides* was unidentified. In 4 cases a micro-aerophilic or anaerobic streptococcus was also grown.

The cultural incubation time in a brain-heart infusion medium varied from 2 to 18 days, one case giving 4 positive blood cultures only after 15 to 18 days' incubation. The source of the infection in 8 cases was the gastro-intestinal tract (the vermiform appendix in 3); 5 other patients pre-

sented with severe pharyngitis and 3 with pneumonia or empyema. *Bacteroides* septicaemia followed pelvic infection in 5 cases (septic abortion in 3, endometritis in one, and a tubo-ovarian abscess in one), and infection of traumatic wounds or decubitus ulcers in 4 cases.

The clinical features were variable, although hectic fever, shaking chills, leucocytosis up to 58,300 per c.mm., and anaemia were usually present. Jaundice was noted in 10 cases, shock in 7, and septic phlebitis in 3. Five of the patients died.

Studies of antibiotic sensitivity suggested that *Bacteroides* was almost always resistant to streptomycin and to penicillin. Two patients developed *Bacteroides* septicaemia shortly after completing a combined course of these antibiotics, 4 had positive blood cultures while treatment was still in progress, and 3 while receiving penicillin alone. Of the 16 cultures tested for sensitivity to tetracycline, all were sensitive, although 2 patients gave positive blood cultures while undergoing treatment with this antibiotic. One of these 2 patients subsequently responded to sulphadiazine. Of the 9 patients treated with a sulphonamide as well as an antibiotic, all recovered, and the authors consider that the most effective treatment of *Bacteroides* septicaemia is a combination of sulphadiazine with a tetracycline.

Finally they offer the following clues to the diagnosis of *Bacteroides* infection: (1) foul-smelling pus containing Gram-negative, rod-shaped organisms with rounded ends, aerobic culture being negative; (2) Gram-negative septicaemia associated with jaundice or shock, with negative blood cultures after 48 hours; (3) thrombophlebitis and septic pulmonary embolism; (4) gas-containing abscesses; (5) abscesses resulting from wounds, or peritonitis contaminated with intestinal or vaginal flora; and (6) fever occurring post-operatively in a patient prepared for colonic surgery with neomycin, kanamycin, streptomycin, or penicillin.

Eirlan Williams

46. Staphylococcal Septicemia Treated with Methicillin: Report of Twenty-two Cases

J. D. ALLEN, C. E. ROBERTS JR., and W. M. M. KIRBY. *New England Journal of Medicine* [New Engl. J. Med.] 266, 111-116, Jan. 18, 1962. 3 figs., 10 refs.

The results obtained with methicillin parenterally in 22 patients with staphylococcal septicaemia are described in this paper from the University of Washington School of Medicine, Seattle. Of the 22 patients, 6 were under 10 years of age, 9 were between 10 and 60 years, and 7 were over 60. In all cases the infections, which were usually associated with debilitating diseases or surgical conditions, were confirmed by blood culture; in 21 cases the staphylococci produced penicillinase. All the organisms were sensitive *in vitro* to 4 µg. of methicillin per ml. Methicillin was given by intramuscular or intravenous injection in an initial dosage of 2 g. 4-hourly, followed by 1 g. 4-hourly when clinical improvement had occurred. In cases of renal insufficiency the dose was reduced and children received 25 mg. per kg. body weight every 4 hours. The average course of treatment lasted 3 weeks (range 8 days to 8 weeks).

Cure was obtained in 16 cases, and in most of these there was dramatic improvement in 24 to 48 hours. One patient, a hydrocephalic infant aged 6 weeks, relapsed, and required two further courses of methicillin and removal of a polyethylene ventricular shunt before cure was achieved. In 5 further patients there was eradication of the infection,

confirmed by negative blood cultures and a fall in temperature, but 4 died subsequently from underlying diseases which were not related to the infection. In the remaining patient in this group a severe hypersensitivity reaction to the drug developed, and another antibiotic had to be given. Only one case in this series was regarded as a treatment failure, the patient dying from an acute myocardial infarction on the third day of methicillin therapy, although in this patient also blood cultures were negative before death.

Side-effects from methicillin, which were minimal, included occasional mild hypersensitivity reactions and slight local tenderness and induration at the site of intramuscular injection. Thrombophlebitis did not follow intravenous administration. Transient azotaemia in 2 patients was attributed to staphylococcal nephrotoxicity and not to the methicillin. The authors draw attention to the high cost of methicillin and the disadvantage of frequent injections; nevertheless they conclude that it is as effective as vancomycin in treating penicillin-resistant staphylococci, without the side-effects so common with the latter drug.

Gerald Sandler

47. Leptospirosis in Bovines and Their Human Contacts in Egypt (U.A.R.)

A. H. HAMDY, W. J. BROWNLOW, and J. D. DEDEAUX. *American Journal of Tropical Medicine and Hygiene* [Amer. J. trop. Med. Hyg.] 11, 98-101, Jan. [received March], 1962. 21 refs.

At the United States Naval Medical Research Unit, Cairo, an investigation was carried out to determine the type and prevalence of leptospiral antibodies in bovines and in human beings having contact with bovines. A total of 1,314 samples of serum were examined, the agglutination lysis test against 12 strains of *Leptospira* being used. Specimens of human sera were obtained from 185 abattoir workers and from 183 farm workers. Only 3 of these were positive—a blood collector had antibodies against *L. grippityphosa* while the specimens from a milker and a herdsman were serologically positive for *L. autumnalis* and *L. malaya* respectively. Specimens of serum were obtained from 367 Indian water buffaloes and 264 dairy cattle from various farms. Leptospiral antibodies were found in 25 (6.8%) of the buffaloes and 8 (3%) of the cattle, as shown in the following table:

Serotypes	Buffaloes	Cattle
<i>L. autumnalis</i>	8	0
<i>L. bataviae</i>	5	1
<i>L. canicola</i>	2	1
<i>L. icterohemorrhagiae</i> A	2	1
<i>L. icterohemorrhagiae</i> AB	8	2
<i>L. malaya</i>	0	3
Total	25	8

Serum samples were also collected at the Cairo slaughterhouse from 191 buffaloes and 124 cattle. Only two specimens, both from buffaloes, were positive, reacting against *L. icterohemorrhagiae* A.B. Attempts to isolate leptospirae from the blood of 15 human beings, 20 buffaloes, and 15 cattle uniformly failed.

It is concluded that the results support the view that leptospirosis is a rare disease in Egypt.

Edward Hiddle

Tuberculosis

48. The Enigma of Tuberculous Peritonitis

S. HYMAN, F. VILLA, S. ALVAREZ, and F. STEIGMANN. *Gastroenterology* [Gastroenterology] 42, 1-6, Jan., 1962. 13 refs.

A definitive diagnosis of tuberculous peritonitis was made on peritoneoscopy or laparotomy in 23 patients "with puzzling systemic and abdominal complaints" seen over 3 years at Cook County Hospital, Chicago. Only 7 of the cases were correctly diagnosed before these procedures were carried out.

The chief presenting symptoms observed were abdominal swelling with or without pain, together with symptoms of systemic infection; the distension being due to ascites in 17 and gas in 6. An enlarged liver (4 cases) and spleen (1 case) were found only in patients with cirrhosis. Laboratory investigations were generally unhelpful, apart from the finding of over 3.5 g. protein per 100 ml. of ascitic fluid, which indicated an exudative process and is seldom found in uncomplicated cirrhosis. Chest radiographs were abnormal in 10 cases. Radiography in another case showed generalized small-bowel disturbance with narrowing of some segments, adhesions, and clumping.

Peritoneoscopy was performed in 20 cases and laparotomy in 3 cases. Typically the peritoneum and small bowel were studied with white nodules; the small bowel was dilated, clumped, and matted together by adhesions to the anterior abdominal wall, with numerous peritoneal pockets. The transverse colon was adherent to the omentum or anterior abdominal wall; the omentum was usually contracted and thickened, appearing as a tumour mass. On biopsy examination of the liver, granulomata were found in only 3 out of 14 cases.

B. Golberg

49. The Chemotherapy of Genitourinary Tuberculosis with Regimens Using Cycloserine

A. S. GURGIS and J. K. LATTIMER. *Journal of Urology* [J. Urol. (Baltimore)] 87, 9-12, Jan., 1962. 3 figs.

Still more efficient antituberculous drug therapy to replace [so far as this is possible] the surgical treatment of genitourinary tuberculosis is constantly being sought. In the present study, carried out at the Presbyterian and Kingsbridge Veterans Administration Hospitals, New York, the authors treated 65 patients with varying degrees of genitourinary tuberculosis with cycloserine, in most cases in combination with PAS and isoniazid. Tuberculous infection was proved by the isolation of "the pathogenic acid-fast bacilli by culture and guinea pig inoculation, from 24 hour collection of urine specimens". Of the 42 male and 23 female patients, whose ages ranged from 7 to 72 years (with the majority in the third and fourth decades), 37 had recent disease and 28 had received other antituberculous drugs, which, however, had been stopped because of intolerance or "bacteriological failure". In 25 cases there was a slight to moderate degree of tuberculous renal damage, while 40 had advanced renal damage, judged radiologically. Of the 42 male patients, 30 had genital tuberculosis either alone or in combination with renal disease. Cycloserine was given in

a dosage of 250 mg. twice daily together with 15 g. of sodium PAS and 300 mg. of isoniazid to 54 patients, the remainder receiving cycloserine with thioban, thiamide, or streptomycin because of intolerance to PAS or isoniazid. In addition, 50 to 100 mg. of pyridoxine was administered to 23 patients in the hope of counteracting the side-effects of cycloserine and isoniazid. The duration of treatment ranged from 7 months to 2 years, 36 patients (54%) having completed 1 to 2 years' treatment.

Of these 36 patients, 35 have shown successful results, as expressed by the absence of tubercle bacilli in one or more of three successive 24-hour urine specimens repeated at 6-monthly intervals and improvement in pyelograms and clinical condition; the remaining patient showed a single isolated positive culture at the end of 2 years' treatment and by the authors' own criteria was regarded as a failure. The remaining patients were still receiving treatment at the time of this report and in none have acid-fast bacilli been isolated from the urine. Of the total series, 57 patients (87.7%) tolerated the drugs well, the other 8 (mostly in the sixth decade of life) had mild intolerance of cycloserine, manifested by dizziness, sluggishness, and loss of equilibrium, while a few developed tremor of the hands or numbness of the fingers and toes; 7 of these 8 patients had not received pyridoxine. Cycloserine was withdrawn when the symptoms occurred. There were no convulsions and no gastro-intestinal disturbances reported. It is concluded that oral cycloserine is a satisfactory and relatively non-toxic adjuvant drug for use in the combined drug treatment of genitourinary tuberculosis. It is recommended that pyridoxine in a dosage of 50 mg. twice daily should be given at the same time.

W. Raymond Parkes

50. Tuberculous Pericarditis. [Review Article]

G. W. H. SCHEPERS. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 248-276, Feb., 1962. Bibliography.

RESPIRATORY TUBERCULOSIS

51. Extrapleural Pneumothorax Combined with Chemotherapy in Pulmonary Tuberculosis. [In English]

T. AAMODT. *Acta tuberculosea et pneumologica Scandinavica* [Acta tuberc. pneumol. scand.] 41, 1-9, 1961. 15 refs.

The author first discusses the relative advantages of extrapleural pneumothorax and of thoracoplasty. He concludes that the former is to be preferred in patients with poor pulmonary function; moreover, it gives better cosmetic results, causes less pain, and there is little interference with the shoulder girdle. He then reports from Glitter Sanatorium, Norway, a follow-up study of 39 patients, 25 male and 14 female, subjected to this procedure between 1953 and June, 1959. They were all sputum-positive on admission, all had cavities, and in 20 cases the disease was bilateral. Some patients were treated by extrapleural plombage with injections of liquid paraffin and others by air instillation; all received the usual antituberculous chemotherapy. No seri-

ous late complications were observed. The author states that at the end of the observation period 37 of the patients (95%) were free of symptoms and were either working or in training; 7 patients (18%), however, had persisting cavities postoperatively or relapsed later.

[Few chest physicians or chest surgeons in Great Britain contemplate extrapleural procedures nowadays.]

Paul B. Woolley.

52. Pneumonectomy without Thoracoplasty in Pulmonary Tuberculosis: a Ten Year Follow-up of Lung and Heart Function

M. W. BOSCH, J. J. HIRDES, G. K. A. OLTROF, and H. M. BEUMER. *Diseases of the Chest [Dis. Chest]* 41, 49-60, Jan., 1962. 6 figs., 10 refs.

The follow-up of lung and heart function of 30 patients treated by pneumonectomy without thoracoplasty has been continued up to 9 years. After an increase over the first years, both V.C. [vital capacity] and T.C. [total capacity] remain constant. The R.V. [residual volume] shows no increase. Although the V.C. is raised, its usable part is somewhat lower than normal resulting in a M.B.C. [maximum breathing capacity] about normal. The influence of the age at pneumonectomy on the lung capacities has been checked. Oxygen saturation and pCO_2 both at rest and during exercise are normal in most cases. At rest the diffusion capacity of the remaining lung is at a level above the normal value for this lung. During exercise the normal maximum level for the diffusion capacity of the remaining lung is reached by the right lung and surpassed by about 20% by the left lung. After pneumonectomy the cardiac output equals the normal value for the cardiac output in the presence of both lungs.

No indication of a progressive emphysematous degeneration of the remaining lung has been found. Reasons are given for considering thoracoplasty a most harmful intervention. After pneumonectomy moderate exercise places a heavy burden on the right heart; this, together with a more restricted ventilation may lead to dyspnea and cor pulmonale in older patients.—[Authors' summary.]

53. Massive Intravenous Therapy as Initial Treatment in Tuberculosis

J. P. MIHALY, E. L. MAIS, S. S. PALEY, S. SCHWARZ, B. W. BILLOW, and B. LUPINI. *Diseases of the Chest [Dis. Chest]* 41, 26-33, Jan., 1962. 2 figs., 15 refs.

The authors report a series of 54 cases treated with intravenous antituberculous therapy at Harlem Hospital, New York, between 1958 and 1960. In 3 cases treatment was discontinued because of thrombosis and in 9 because the patient failed to cooperate. Of the remaining 42 patients, 5 had miliary and meningeal, one renal, and 36 pulmonary tuberculosis, and ages ranged from 13 months to 70 years, most patients being in the 4th and 5th decades. All were given intravenous therapy continuously for up to 6 weeks. This consisted in the daily administration by drip infusion of 1 litre of fluid in which were dissolved 1 or 2 g. of dihydrostreptomycin pantothenate, 12 g. of a soluble PAS preparation, and 5 to 10 mg. of soluble isoniazid per kg. body weight, together with the necessary heparin, the flow rate being adjusted so that administration extended over the 24 hours. After the period of infusion treatment patients were given 1 g. of dihydrostreptomycin pantothenate thrice

weekly intramuscularly and 300 mg. of isoniazid and 12 g. of PAS orally each day. The total duration of treatment was between 5 and 9 weeks (average 46 days). The authors claim "phenomenal efficacy" in producing clinical and bacteriological remission within 2 weeks and reducing the stay in hospital to an average of 3 months.

[Few figures are given, but it would appear that the standard method of treatment used in Great Britain produces comparable results without the risks attending intravenous therapy. It is of interest to note that such treatment was, however, carried on continuously for 6 weeks and often in ambulant patients.]

Janet Q. Ballantine

54. Oral Hypoglycemic Agents in Diabetic Patients with Pulmonary Tuberculosis

F. GUROL, S. S. ADELSON, N. H. DEJANNEY, and P. T. CHAPMAN. *American Review of Respiratory Diseases [Amer. Rev. resp. Dis.]* 85, 51-57, Jan., 1962. 2 figs., 25 refs.

Oral hypoglycaemic drugs were given alone or in combination with insulin to 65 tuberculous diabetic patients at Herman Kiefer Hospital, Detroit. In a total of 74 treatments the patients received tolbutamide alone, chlorpropamide alone, phenformin alone, or phenformin combined with insulin. In 56 instances the response was "excellent" or "good" and in 5 it was "fair"; treatment failed in 13. The authors state that the hypoglycaemic drugs had no significant side-effects and did not impair healing of the tuberculous disease.

C. M. Fletcher

55. Cavitated Pulmonary Tuberculosis: a Long-term Follow-up of 283 Patients with Special Reference to the Significance of the Persistent Cavity

P. G. ARBLASTER, K. W. CROSS, I. R. MCWHINNEY, and J. YATES. *Tubercle [Tubercle (Lond.)]* 42, 428-437, 1961. 2 figs., 19 refs.

A follow-up study of 283 patients with cavitated pulmonary tuberculosis who were first diagnosed between 1946 and 1955 and who received no major surgery is presented from Warneford Hospital, Leamington Spa, Warwickshire. There were 123 deaths in the series (44%), of which 108 (88%) were the direct result of pulmonary tuberculosis (15 being from other causes), but most (93) of these deaths occurred before 1951; 61% of the patients who died from tuberculosis had not received any chemotherapy. Six survivors of the series showed radiographic deterioration and in a further 6 the sputum was still positive at the time of final assessment. Relapse occurred in 34 cases; apart from 9 who were uncooperative, all these patients had received insufficiently prolonged chemotherapy and all responded to a second course of treatment without further relapse.

A separate analysis is made of 55 patients with persistent cavitation who were alive at the end of 1956 and who at that time were receiving prolonged chemotherapy. Of these, 40 were alive at the end of 5 years, while of the 15 who died, 5 did so from active tuberculosis, 5 from complications of quiescent tuberculosis, and 5 from other causes. The overall mortality was 47% in the period 1946-51, but only 12% in the period 1952-5; there was a direct relationship between increasing age and death rate. The authors conclude that in patients with drug-sensitive organisms who are willing to undergo long-term chemotherapy neither initial cavitation nor the persistence of cavitation is in itself an indication for alternative methods of treatment.

G. M. Little

Venereal Diseases

56. An Evaluation of the Reiter Protein Complement-Fixation Test in the Diagnosis of Syphilis

R. B. PATTON and A. GAURIE. *American Journal of Clinical Pathology* [Amer. J. clin. Path.] 36, 383-389, Nov., 1961. 3 figs., 14 refs.

This report from the Henry Ford Hospital, Detroit, analyses the results obtained with the Reiter protein complement fixation (R.P.C.F.) test as a confirmatory procedure in routinely performed serological tests for syphilis. Over a 2-year period 77,672 sera were screened by means of the V.D.R.L. slide test and any sera found to be reactive were re-examined by a quantitative Kolmer and the R.P.C.F. tests. Of 680 sera giving a positive result with the V.D.R.L. test, 48.9% were reactive with both the Kolmer and R.P.C.F. tests, 19.1% gave a positive reaction with the Kolmer test but were negative with the R.P.C.F. test, 15.7% were negative by both tests, and the remaining 16.3% gave a negative Kolmer test result but were positive with the R.P.C.F. test. From the examination of the hospital records of these 680 patients, 424 were judged to be suffering from syphilis at various stages. In this group the Kolmer test was positive in 326 (77%) and the R.P.C.F. test positive in 343 (81%). In 99 cases the results were considered to represent biological false positive reactions, and of these the Kolmer test was positive in 46 and the R.P.C.F. test in 16. There was insufficient clinical information available for an evaluation of the status of the remaining 157 patients.

The authors conclude that when both the Kolmer and the R.P.C.F. tests are positive, in addition to the V.D.R.L. screening test, the chance of the reaction being non-specific is less than 5%. They consider that the R.P.C.F. test is valuable as a secondary screening test, or even as a definitive test for syphilis, because of the low incidence of false positive reactions that it gives.

A. E. Wilkinson

57. Some Aspects of Congenital Syphilis in the Neonatal Period. (Alguns aspectos da lues congênita no período neonatal)

S. SCHVARTSMAN, J. L. A. RAMOS, and H. B. CORRADINI. *Pediatria prática* [Pediat. prat. (S. Paulo)] 32, 185-192, 1961. 10 refs.

The authors report that among 1,392 infants born at the Hospital of the University of São Paulo, Brazil, during the period January to September, 1960, there were 8 cases of congenital syphilis (0.58%). They state that because of the prevailing indiscriminate use of antibiotics, particularly penicillin, congenital syphilis in the neonatal period now tends to present without the classic "exuberant" physical signs of the disease. They then widened their study to include 58 cases of congenital syphilis seen between 1945 and 1960, in which the diagnosis was beyond doubt and had been made in the first 30 days of life. Of the 30 babies with a birth weight of less than 2.5 kg., 25 died. In the whole series 30 babies died, 8 within the first 24 hours of life, 2 within 48 hours, and 20 at various later times.

Clinical signs of syphilis were evident in 44 cases, no such evidence was obtained in 6, and the remaining 8 babies died before they could be examined. The commonest signs were

splenomegaly (23 cases), hepatomegaly (21), skin lesions (21), jaundice (18), oedema (16), and rhinitis (6). The results of liver function tests, haematological studies, serum protein analyses, and determination of serum bilirubin levels are presented in a series of tables.

Of the 30 babies who died, all of whom came to necropsy, osteochondritis was present in 27, underlining the importance of radiological examination as a diagnostic measure (periosteitis, however, occurred in only one case). Splenomegaly was found in 23 cases, pneumonia in 8, hepatomegaly in 7, and jaundice in 6.

Eric Dunlop

58. Dosage of Penicillin for Acute Gonorrhoea of Males

L. D. SABATH and J. J. KIVLAHAN. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 242, 663-672, Dec., 1961. 1 fig., 33 refs.

The authors describe the results obtained with penicillin in different dosage schedules in the treatment of acute gonorrhoea in 507 members of the United States Army stationed in Korea in 1958 and 1959. Of 103 patients given 3 daily injections, each of 600,000 units, of procaine penicillin in oil with aluminium monostearate, 62 were cured and 41 did not respond, a failure rate of 40%. A further course of 6 daily injections of 600,000 units of the same preparation was given to 9 of those who failed to respond, with cure in 5. Of 107 patients given 600,000 units of aqueous procaine penicillin daily for 3 days, 89 were cured, giving a failure rate of 17%. In a group of 144 patients receiving a single injection of 1.2 or 1.5 mega units of aqueous procaine penicillin the failure rate was 17% also, while in 153 given 1.5 mega units of the same preparation daily for 3 days the failure rate was only 6.5% (10 failures). Of 53 of the patients who had failed to respond to procaine penicillin, 4 (7.5%) also showed no response when 2 injections, each of 900,000 units, of the same preparation were given 3 hours apart on 2 consecutive days.

It is noted that there were fewer failures when the dosage regimen resulted in a high serum level of penicillin. In view of reports of the declining sensitivity of the gonococcus to penicillin this is considered significant.

R. R. Willcox

59. Therapy of Lymphogranuloma Inguinale with 17,025

C. D. ALERGANT. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 37, 270-272, Dec., 1961 [received Feb., 1962]. 5 refs.

A new synthetic anti-viral agent, 5-methoxy carbonyl-6-methyl-4-(5-nitrofuryl)-2-oxy 1:2:3:4-tetrahydropyrimidine, provisionally termed 17,025, was tried at Newsham General Hospital, Liverpool, in the treatment of 9 patients with lymphogranuloma inguinale (venereum). The total dose varied from 2 to 10 g., this being given in intramuscular injections of 0.5 g. to 2 g. once or twice a week. No evidence of toxicity was observed. A satisfactory result was obtained initially in 8 patients, 2 of whom, however, subsequently relapsed. One patient failed to respond. The author concludes that this drug appears to be a useful agent against lymphogranuloma inguinale (venereum) but that the optimum dosage has yet to be determined.

Leslie Watt

Tropical Medicine

60. Results of Laboratory and Field Trials with the Molluscicide Bayer 73

R. GÖNNERT. *Bulletin of the World Health Organization* [Bull. Wld Hlth Org.] 25, 483-501, 1961 [received March, 1962]. 1 fig., 13 refs.

The author, writing from the Chemotherapy Institute of Farbenfabriken Bayer A.G., Wuppertal-Elberfeld, Germany, where during 10 years he has tested more than 20,000 drugs for molluscicidal efficacy, reviews laboratory and field trials [see also Abstracts 61 and 62] of the synthetic molluscicide dichloro-5:2'-nitro-4'-salicylanilide (Bayer 73). He considers this preparation to be superior to other molluscicides, laboratory investigations having shown it to be lethal to snails which harbour *Schistosoma* and *Fasciola* in a concentration as low as 0.2 to 0.5 part per million (p.p.m.). It destroys both adult snails and ova, also cercariae and miracidia of the parasite, but is innocuous to warm-blooded animals and plants, though toxic to fish. Application to a stream of 1 p.p.m. is effective for 5 to 8 miles downstream and ensures freedom from snails for one to 3 months. The compound is less effective in muddy and still waters, as is also the case with sodium pentachlorophenate, but it can be used in one-tenth the concentration of the latter.

Clement C. Chesterman

61. Laboratory and Field Trials of a New Molluscicide, Bayer 73, in Tanganyika

G. WEBBE. *Bulletin of the World Health Organization* [Bull. Wld Hlth Org.] 25, 525-531, 1961 [received March, 1962]. 9 refs.

Enclosed waters such as fishponds play an important part in spreading schistosomiasis in Tanganyika, where no large irrigation schemes exist. The present paper describes a series of trials in a number of fishponds, and in the laboratory designed to compare the molluscicidal activity of Bayer 73 [see Abstract 60] with that of sodium pentachlorophenate, using 70% and 90% wettable powders respectively. It was found that a concentration of 3 p.p.m. of the pentachlorophenate was required to kill off the 6 common species of snail which act as vectors of the schistosome, whereas only 0.3 p.p.m. of Bayer 73 was necessary. Snails reappeared in 8 to 9 weeks. Small fish and frogs were killed, but vegetation was only slightly affected. Bayer 73 is therefore considered to be a useful new weapon in the control of schistosomiasis.

Clement C. Chesterman

62. Trials with a New Molluscicide, Bayer 73, in Southern Rhodesia

C. J. SHIFF. *Bulletin of the World Health Organization* [Bull. Wld Hlth Org.] 25, 533-542, 1961 [received March, 1962]. 1 fig., 8 refs.

This paper reports an investigation of the efficacy of Bayer 73 [see Abstract 60] as a molluscicidal agent in the control of schistosomiasis in Southern Rhodesia. Laboratory tests against local snail vectors gave satisfactory results, a concentration of 0.5 p.p.m. being fully effective against the snails and their ova and against the cercariae of *Schisto-*

soma. Field tests in shallow ponds showed that concentrations were well maintained for 72 hours, producing a 100% mortality. Equally good results were obtained with larger reservoirs, which were treated from a rowing-boat fitted with a small pump-operated spray. Spraying from a helicopter was also tried, and it is suggested that this method should prove useful for larger collections of water or more inaccessible regions.

Clement C. Chesterman

NUTRITIONAL DISORDERS

63. The Heart in Kwashiorkor

P. M. SMYTHE, A. SWANEPOEL, and J. A. H. CAMPBELL. *British Medical Journal* [Brit. med. J.] 1, 67-73, Jan. 13, 1962. 11 figs., 23 refs.

The authors present from the University of Capetown a clinical and pathological study of the heart in kwashiorkor, based on the investigation of 98 children, of whom 65 recovered and 33 died. Electrocardiograms (ECGs) were always obtained, serial tracings being available in many cases. Standard chest radiographs were taken in 62 cases, while serum potassium levels were determined in 77 cases and serum calcium levels in 9. Post-mortem examination was carried out in 24 of the fatal cases. After admission most of the patients were treated with a broad-spectrum antibiotic; some were given penicillin or sulphadiazine for the first 7 to 10 days and all received 1 g. of potassium and a vitamin preparation by mouth daily. For the first day half-strength Darrow's solution only was administered orally, but thereafter the child was given for 2 or 3 days skimmed, half-cream, and full-cream milk successively and finally a full diet.

Infallible signs of congestive cardiac failure, such as filling of the neck veins, are rare in kwashiorkor and the authors regard oedema and hepatomegaly as part of the nutritional deficiency syndrome. Sudden unexpected death during what appears to be a recovery phase is one of the most striking features of the disease. In 49 cases x-ray examination showed the heart to be abnormally small. The cardiothoracic ratio was low, but increased to 0.5 or more with recovery. ECG studies revealed a tendency to sinus tachycardia, with rates up to 200 or more per minute. Of 3 patients with bradycardia, 2 suffered from hypothermia. Various bizarre ECG patterns are described. An "ionic" pattern occurs in which a deep S-T depression with prolongation of the Q-Tc interval correlates well with hypopotassaemia. Of the children showing this pattern, 6 who recovered had serum potassium levels of 2 to 2.9 mEq. per litre and 4 who died had levels of 1.4 to 2 mEq. per litre. The pattern could be corrected within 48 hours by giving potassium by mouth. One of these patients had a serum calcium level of 6 mg. per 100 ml. A pattern of low voltage with flat T waves was seen in 19 patients, of whom 10 died. A sharp T-inversion in the precordial leads was noted in a group of 6 cases, of which one was fatal. A complex recovery pattern characterized chiefly by elevation of the

ST segment, particularly in standard Lead II and in Leads V2 to V4 is described. In 2 hypothermic cases the characteristic ECG of cold injury manifested by low voltage and prolonged Q-Tc was observed. Normal ECGs were recorded in 8 patients, 2 of whom died from tuberculosis.

In 15 out of 16 children followed up the ECG showed a normal pattern one year later. In 18 of the 24 cases examined post mortem an adequate cause of death was established. The most striking feature of the cardiac pathology was underweight of the heart; hearts weighing 23 g. at age 16 months and 32 g. at 2 years are mentioned. Microscopical appearances were normal in most cases. In 4 cases there was oedema, the fibres being separated by palely staining eosinophilic fluid. Discussing the sudden unexpected deaths, the authors consider that potassium deficiency can hardly account for these, as death occurred in the recovery phase when the potassium deficiency had already been corrected. The mobilization and excretion of large quantities of extracellular fluid which contains up to 0.5 g. of protein per 100 ml. may be an important factor in causing arrest of a heart already weakened by the general malnutrition.

William Hughes

64. Erythroid Hypoplasia in Kwashiorkor

F. WALT, J. E. D. TAYLOR, F. B. MAGILL, and A. NESTADT. *British Medical Journal* [Brit. med. J.] 1, 73-75, Jan. 13, 1962. 1 fig., 12 refs.

At the McCord Zulu Hospital, Durban, the authors have studied erythroid hypoplasia in kwashiorkor. The condition, which is characterized by a temporary fall in the haemoglobin level and a diminution or complete disappearance of reticulocytes, occurs during the recovery phase of the disease treated in hospital. Some observers believe it to be due to riboflavin deficiency. The authors have treated 46 patients with different basic diets plus in all cases vitamin and mineral supplements, as follows. Group 1 (16 patients) received skimmed milk; Group 2 (15 patients) were given "nutrofood", a cereal-like preparation containing 21.5 g. of protein, 5.3 g. of fat, and 57.6 g. of carbohydrate per 100 g.; Group 3 (15 patients) received "nutrofood" plus maize meal. All the patients were also given chloramphenicol, potassium, folic acid, and a multivitamin syrup containing vitamin A, most of the B-complex vitamins (including 0.75 mg. of riboflavin daily), and vitamin C.

Erythroid hypoplasia developed in 7 cases, 2 in Group 1, 1 in Group 2, and 4 in Group 3. Reticulocytes were absent from the blood some time between the 18th and 30th days of treatment. One case showed 2 hypoplastic phases, one on admission and a second on the 27th day. A spontaneous reticulocytosis of 7% or more occurred within 9 to 12 days of the hypoplastic period. The haemoglobin level fell in one instance from 7.4 to 4.8 g. per 100 ml. within 2 days; in the other cases falls occurred, but were insignificant. The bone-marrow pictures varied, but in some cases a complete absence of erythroid elements was noted for a time. Discussing the cause of the phenomenon the authors point out that a tremendous change in metabolism occurs in the first 3 weeks of treatment. This involves a marked diuresis, often a loss of potassium, retention of sodium, and an increase in all the plasma proteins. Possibly some imbalance occurs at this time, leading to a deficiency of some factor essential for erythropoiesis. In this series it was impossible to exclude chloramphenicol as a cause, but the authors do not

consider it likely. A deficiency of riboflavin can be excluded since the diets contained not less than 0.75 mg. daily.

William Hughes

INFECTIOUS DISEASES

65. Status of Typhus in Lebanon

R. M. MATOSSIAN, G. A. GARABEDIAN, and A. H. MALAKIAN. *American Journal of Tropical Medicine and Hygiene* [Amer. J. trop. Med. Hyg.] 11, 104-107, Jan. [received March], 1962, 9 refs.

In this study of the epidemiology of typhus in the Lebanon, which has not previously been investigated, 454 specimens of serum were collected from students and hospital patients at the American University of Beirut, of which 50 were from students and well-to-do people and the remainder from poorer individuals; all the subjects were of Lebanese nationality. Serum was also collected from 51 rats trapped in Beirut, all of which were infested with fleas. Complement fixation (CF) tests were performed on the sera, using an antigen prepared from eggs infected with *Rickettsia prowazekii*, Strain E. The human sera were also tested by a haemagglutination (HA) technique.

Of the human sera, 16.74% gave a positive CF reaction and 8.15% were positive in the HA tests. Of the rat sera, 35.3% gave a positive CF reaction. The authors confirm that the CF test is more reliable than the HA test for detecting residual antibodies to typhus. HA antibodies disappeared from the circulation within a few months of the illness, whereas CF antibodies were still present after 30 years. There was a stepwise increase of the rates of infection in the older age groups, suggesting a slow but continuous level of exposure to the disease. The high incidence of murine typhus among the rats suggests that they may be the source of the human infections.

L. G. Goodwin

65a. O'Nyong-nyong Fever: an Epidemic Virus Disease in East Africa. V. Human Antibody Studies by Plaque Inhibition and Other Serological Tests

M. C. WILLIAMS, J. P. WOODALL, and J. S. PORTERFIELD. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [Trans. roy. Soc. trop. Med. Hyg.] 56, 166-172, March, 1962. 10 refs.

66. "B 663" in the Treatment of Leprosy: Preliminary Report of a Pilot Trial

S. G. BROWNE and L. M. HOGERZEIL. *Leprosy Review* [Leprosy Rev.] 33, 6-10, Jan.; 1962. 8 refs.

The authors present a preliminary report of a trial of a new rimino compound "B663", a substance which has been shown to be more active in the treatment of experimental tuberculosis in laboratory animals than any compound hitherto investigated. Given orally or parenterally it is absorbed and taken up unchanged by living mycobacteria. In excessive dosage it is deposited in crystalline form in the reticulo-endothelial system of animals where it promotes a foreign body reaction, but exerts no further toxic effect.

The present trial, reported from Uzuakoli, Eastern Nigeria, was confined to 16 patients, 14 with lepromatous leprosy and 2 with border-line disease, who were divided into three groups as follows: (1) 3 patients received standard doses of

dapsone in addition to B663; (2) 8 patients were given B663 only; and (3) 5 patients received daily inunction with 5 ml. of "etisul" liquid (ditophal) in addition to B663. The dosage of B663 was regulated according to body weight, ranging from 0.1 g. daily in a patient weighing 50 lb. (22.7 kg.) to 0.3 g. daily for 10 patients with an average weight of 116 lb. (52.7 kg.), the drug being given in crystalline form by mouth in a capsule with one teaspoonful of groundnut oil. The trial lasted 6 months. A peculiar ruddiness of the skin developed in all 16 patients, in some cases progressing to a generalized hypermelanosis. Areas of lepromatous skin did not develop these pigmentary changes. It was noted that a breast-fed baby developed a similar redness while its mother was receiving B663. In spite of this, however, the child developed hypopigmented patches suggestive of early leprosy 5 months after the end of the trial. No toxic effects were observed beyond a slight transient nausea and giddiness in 2 patients who were receiving the higher dosage. Over-all there was considerable improvement in the 11 patients in Groups 1 and 2, while 2 of the 5 patients in Group 3 were considerably improved. Improvement, which was most marked in Group 1, that is, combined B663 and dapsone, was manifested by a reduction in the size and elevation of existing lepromata, some repigmentation of macular areas, and bacteriological signs of regression. The bacterial index decreased by 49% in the 3 patients whose treatment was supplemented with dapsone. The authors consider these preliminary results to justify further trial of rimino compounds in leprosy.

William Hughes

67. **Initial Results of a Trial of Ciba 1906 in DDS-Intolerant and Reaction-prone Leprosy Cases in Korea**
J. S. KIM and S. C. TOPPLE. *Leprosy Review* [*Leprosy Rev.*] 33, 20-24, Jan., 1962. 2 refs.

This preliminary trial of "Ciba 1906" (diphenylthiourea) was carried out at Soonchun, Korea, on 33 patients with leprosy, all of whom had shown symptoms of reaction or intolerance on treatment with dapsone (DDS). The median duration of the disease was 6 years, but was over 10 years in 6 cases. The leprosy was of the active lepromatous type in 32 cases and a lepra reaction had been observed in all except one case. In many cases the reaction was severe and 27 of the patients had received oral corticosteroid therapy for this complication at some time. The initial dosage of Ciba 1906 was 0.5 g. daily for 4 to 6 weeks. If no reaction occurred the dose was increased to a maximum of 1.5 g. daily, previous reports having shown the drug to be safe up to a dosage of 8.0 g. daily. Response to therapy was assessed on clinical grounds. In 11 patients a favourable result was obtained, but in 17 the results were poor and the drug had to be discontinued. Since standard treatment had previously failed in all cases, it is considered that the favourable response in one-third of these difficult cases justifies further trials of the drug.

William Hughes

68. **Some Newer Amoebicides in Acute Amoebic Dysentery**
A. J. WILMOT, S. J. POWELL, I. MCLEOD, and R. ELSDON-DEW. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [*Trans. roy. Soc. trop. Med. Hyg.*] 56, 85-86, Jan., 1962.

In an investigation reported from the University of Natal, Durban, 4 new amoebicides were tested in acute amoebic dysentery and the results compared with those obtained

with tetracycline and with emetine followed by emetine bismuth iodide. It was found that diloxanide ("entamide") and its furoate salt ("furamide"); chlorphenoxamide ("mebinol"), and phanquone ("entobex"), a phenanthroline compound, were less effective than the standard drugs. Paromomycin ("humatin") was effective at high dosage (3 g. per day), but ulcers healed more slowly than with tetracycline.

R. A. Neal

69. **Studies in the Epidemiology of East African Leishmaniasis. 1. The Circumstantial Epidemiology of Kala-azar in the Kitui District of Kenya**

B. A. SOUTEGATE and B. V. E. ORIEDO. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [*Trans. roy. Soc. trop. Med. Hyg.*] 56, 30-47, Jan., 1962. 7 figs., 27 refs.

A few cases of kala-azar were first detected in the Kitui district of Kenya in 1946, after which the disease spread southward and eastward. Its incidence gradually rose from 13 cases in 1951 to 581 in 1960, but, since parasitological diagnosis was practised only from 1957, the previous findings might have been inaccurate. The age distribution of patients with the disease depends upon the degree of its endemicity: in old-established foci the adults have acquired immunity, with the result that mainly children are affected, whereas in new foci the incidence is higher among adults, males being predominantly affected.

In the present study a survey of the environmental conditions of the people and of the distribution of homesteads affected by kala-azar showed a random distribution, with only 1 or 2 cases per homestead. No definite correlation between the incidence of kala-azar and the presence or absence of domestic animals occupying human dwellings could be established, and though the incidence was higher among people sleeping along with their animals in the huts, this might have been due to the prevailing insanitary conditions. On the other hand, the incidence was significantly higher in homesteads situated near termite hills, since in such cases there is the risk of being bitten by sandflies emerging from the termitaries. In the course of 2 years only 9 cases of post-kala-azar dermal leishmaniasis were observed, representing about 1.8% of all treated cases. This condition is therefore not regarded as an important source of infection. The authors attach greater significance in man-to-man transmission to untreated early cases.

C. A. Hoare

70. **Oral Tartar Emetic in the Treatment of Schistosomiasis**

D. M. FORSYTH and W. T. SIMPSON. *Annals of Tropical Medicine and Parasitology* [*Ann. trop. Med. Parasit.*] 55, 410-412, Dec., 1961 [received Feb., 1962]. 9 refs.

In view of the good results reported by Mao *et al.* (*Chin. med. J.*, 1959, 78, 532) with antimony potassium tartrate (tartar emetic) in the treatment of schistosomiasis, 5 Arab patients, 4 adults with *Schistosoma haematobium* infection and one boy aged 13 with *S. mansoni* infection, were treated with tartar emetic given orally in cellulose-coated tablets. The adults received 30 mg. in divided doses on the first day, 60 mg. on the second, 160 mg. on the third, and 300 to 400 mg. daily for the remainder of the course, which lasted for 17 days, the total dosage varying from 100 to 120 mg. per kg. body weight; the boy received approximately one half this dosage.

Blood antimony levels of 0.2 mg. per 100 ml. were obtained, but in no case did clinical cure result. No clinical side-effects were noted, except that one of the 4 patients tested showed an abnormal electrocardiogram. Expressing their disappointment with these results—Mao *et al.* claimed a cure rate of 60%—the authors remark that “schistosomiasis is a major problem in many countries, and its successful treatment by means of a cheap oral preparation would represent a great advance”.

R. R. Willcox

71. A Trial with Dehydro-emetine in Schistosomiasis in Rhodesia

M. GELFAND, E. T. REID, and B. E. SIMPSON. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [Trans. roy. Soc. trop. Med. Hyg.] 56, 77–80, Jan., 1962. 7 refs.

In view of the partial success obtained with emetine in the treatment of schistosomiasis the authors, at Harari African Hospital, Southern Rhodesia, have tried a synthetic analogue, Ro 1-9334 (2:3-bis-dehydroemetine hydrochloride). The drug was given intravenously in a dosage of 1.5 mg. per kg. daily for 10 days to 16 African patients infected with *Schistosoma haematobium*. Cure ensued in 11 patients as shown by the absence of eggs in the urine on examination 3 months after completion of treatment. No toxic side-effects were observed. In a further 4 patients infected with *S. mansoni* in addition to *S. haematobium* the treatment had no effect on the *S. mansoni* infection, as all 4 patients were passing eggs 4 months after treatment was concluded.

R. A. Neal

72. Bilharziasis in Tanganyika: Observations on Its Effects and the Effects of Treatment in Schoolchildren

P. JORDAN and K. RANDALL. *Journal of Tropical Medicine and Hygiene* [J. trop. Med. Hyg.] 65, 1–6, Jan., 1962. 15 refs.

All boys, aged 12 to 19 years, at a boarding school near Mwanza on Lake Victoria, Tanganyika, were examined in an attempt to relate infection with *Schistosoma mansoni* or *S. haematobium* to blood haemoglobin values, liver and spleen enlargement, height, weight, exercise tolerance, and scholastic ability. Transmission of *S. mansoni* in the area occurs on the shores of Lake Victoria and frequent reinfection is inevitable. *S. haematobium* transmission is seasonal and widespread, and is dependent on the filling of temporary water-holes in the rainy season.

Boys found to be infected with *S. haematobium* were treated with lucanthone hydrochloride or “TWSb” (sodium antimonyl dimercaptosuccinate) and any changes in physique and scholastic ability were estimated 6 months after treatment. A group of boys who refused treatment served as controls. Examination of the urine and stools for ova and C.H.R. (cercaric-hüllen reaction) tests on the serum showed an over-all incidence of bilharziasis of 83%. Rectal biopsy would probably have detected a still higher rate of infection. The C.H.R. test was less sensitive in the older than in the younger boys. Ova of hookworms (*Necator* and *Ancylostoma*) were found in 39% of the children. Boys infected with *S. mansoni* only or hookworms only showed significantly lower haemoglobin values and were smaller and weighed less than those who were not passing ova in the stools. Concurrent infections with both *S. mansoni* and hookworms were frequent. The haemoglobin values of boys infected with *S. haematobium* did not differ significantly from

uninfected controls, but their exercise tolerance was lower. Children infected with *S. haematobium* were apparently more intelligent than those who were not [the chances of exposure to infection are probably greater for the more enterprising boys]; both exercise tolerance and scholastic ability improved after treatment with schistosomicidal drugs.

In the age-groups examined, neither liver nor spleen enlargement was associated with *S. mansoni* infection.

L. G. Goodwin

73. Ascariasis and Peptic Ulcer in Radiology

K. S. HUQUE and N. ISLAM. *Journal of Tropical Medicine and Hygiene* [J. trop. Med. Hyg.] 65, 6–9, Jan., 1962. 4 figs., 4 refs.

An additional radiograph taken 2 to 3 hours after a routine barium meal often shows the presence of *Ascaris* in the small intestine of patients in the tropics. In this paper, 4 photographs illustrate the appearance of the shadows cast by the worms in such skiagrams. At Dacca Medical College Hospital, East Pakistan, the authors have studied 162 patients with a clinical diagnosis of peptic ulcer. *Ascaris* eggs were present in the stools of 50 of these patients, while worms were detected radiologically in 88. Of the 90 patients in the group shown to have organic lesions, 42 also had radiological evidence of ascariasis.

The authors recommend that *Ascaris* should always be looked for during the radiological examination of patients with suspected peptic ulcer.

L. G. Goodwin

74. Treatment of Ancylostomiasis with Bephenium Salts in Japan

S. IWATA, G. UEDA, T. ARAKI, K. TAKI, and T. KAGEYAMA. *Journal of Tropical Medicine and Hygiene* [J. trop. Med. Hyg.] 65, 9–11, Jan., 1962. 13 refs.

Most of the inhabitants of Mikayama, near Osaka, Japan, work in tangerine orange orchards. Examination of the stools of 696 of these workers showed hookworm ova in a single direct smear in 5.5%, while a flotation technique detected ova in 10.3%. Common complaints among those infected were headache, general malaise, weakness, and nausea. Both *Ancylostoma* and *Necator* were present, but the latter was relatively uncommon, almost all the patients harbouring *Ancylostoma* only.

Treatment with a single dose of 5 g. of bephenium hydroxynaphthoate resulted in a complete clearance in 92% of the patients, this being confirmed by the flotation method. When saline purge was given the night before, and again 2 hours after the bephenium, the clearance rate was 88.9%. [These percentages are based on groups of only 25 and 18 patients respectively. The difference represents 2 patients in each group who were not completely freed from hookworm ova and is not significant.] A third group of 9 patients who were given “wormin” (1-bromo-2-naphthol) in a dosage of 3 g. twice daily for 2 days showed a clearance rate of 78%. [Two of the patients still passed hookworm ova]. Side-effects of bephenium (slight nausea, headache, dizziness, abdominal pain, and diarrhoea) were observed more frequently in the group which was also given saline purgatives.

The authors conclude that bephenium hydroxynaphthoate seemed to be an excellent compound for the mass treatment of hookworm infection.

L. G. Goodwin

Allergy

75. Response of Nonallergic Persons to Injected Castor Bean Allergen, CB-1A

J. R. SPIES and H. S. BERTON. *Journal of Allergy* [J. Allergy] 33, 73-83, Jan.-Feb., 1962. 2 figs., 22 refs.

The effect of injection of castor bean antigen in 161 non-allergic inmates of the District of Columbia Workhouse, Occoquan, Virginia, was tested by the Prausnitz-Küster and reagin neutralization methods. Most of the subjects (132) received 1 to 5 consecutive weekly injections of 1 mg. of antigen, and only 4 of them had mild clinical symptoms in response. Of 23 subjects receiving two or more courses of 1 to 5 weekly injections, 15 either lost the capacity to give a passive transfer reaction (which the authors regard as evidence of the formation of blocking antibody) or developed clinical symptoms (itching, rash, and swelling at the site of injection); there were no respiratory symptoms. In one subject skin sensitivity developed and reagins were present in the serum.

H. Herxheimer

76. The Treatment of Bronchial Spasm with a Combination of Three Standard Drugs in a Slow-release Presentation ("Expansyl")

H. J. PHIN and D. V. SALKELD. *British Journal of Diseases of the Chest* [Brit. J. Dis. Chest] 56, 23-25, Jan., 1962. 3 refs.

The authors describe a therapeutic trial in bronchial spasm of a "spansule" capsule containing 5 mg. of diphenylpyraline (an antihistamine), 50 mg. of ephedrine sulphate, and 2 mg. of trifluoperazine (a tranquillizer). One spansule was prescribed night and morning for 51 patients with bronchial asthma and 15 with chronic bronchitis and asthma. All the patients had been under observation for some time and it was assumed that their previous experience with symptomatic remedies would enable them to assess the effect of the new preparation. Of the asthmatic patients, "excellent" results were claimed by 19; "good" results by 22, and "fair" by 7; in 3 patients the preparation was without effect. Of the patients with emphysema and chronic bronchitis, 5 experienced an "excellent", 5 a "good", and 3 a "fair" response; in 2 there was no effect. The convenience of the long-acting preparation is stressed. Side-effects, which were negligible, included drowsiness, present in 2 patients, dizziness in one, dry mouth in 4, and transient palpitations in 4.

[The value of these observations is diminished because no control group treated with a standard preparation was available for comparison by the double-blind technique.]

R. S. Bruce Pearson

77. Immunological and Clinical Responses to Repository Ragweed Pollen Therapy—a Two Year Study. [In English]

L. H. CRIEP, H. FRIEDMAN, and P. BLANK. *International Archives of Allergy and Applied Immunology* [Int. Arch. Allergy] 20, 1-24, 1962. 2 figs., bibliography.

Ragweed emulsion therapy was given to 481 patients with ragweed hay-fever in 1959 and to 297 patients in 1960. The various treatments differed in that in 1959 multiple

aqueous treatment was compared with emulsion therapy, and in 1960 untreated patients were given 4 to 7 primary doses of aqueous pollen extract before receiving intramuscularly 25 to 35 times the maximum dose of aqueous extract as an emulsion.

It was found that the 440 patients who received a repository injection of a pollen extract emulsified in a mineral oil obtained clinical relief comparable to that experienced by the 347 patients given the conventional aqueous therapy. General reactions occurred in 2% to 4% of patients, but no delayed hypersensitivity reactions were seen. No correlation was found between the clinical results and any changes in conjunctival threshold sensitivity, or with increases in the titre of blocking and haemagglutination antibodies.

A. W. Frankland

78. Cow's Milk Allergy in Infants and Children. [In English]

C. COLLINS-WILLIAMS. *International Archives of Allergy and Applied Immunology* [Int. Arch. Allergy] 20, 38-59, 1962. Bibliography.

The incidence of cow's-milk allergy is difficult to estimate, as in a selected series of allergic children the figure may be reported as 30%, while in non-allergic children it is reported as less than 0.1%. It is certainly an extremely important and significant form of allergy seen in infants and young children.

The classic nomenclature of the past referred to the milk proteins as casein, lactalbumin, and lactoglobulin, but these are now referred to as α -casein, β -lactoglobulin, and α -lactalbumin. These 3 proteins make up 54 to 80% of the total protein of skimmed milk, with β -lactoglobulin the most allergenic. Heating cow's milk decreases its allergenicity unless the patient is sensitive to the heat-stable α -casein, but heating does not uniformly alter the heat-denaturable proteins and some allergenicity of different fractions may remain. This means that for the extremely sensitive patient heat-modified cow's (or goat's) milk is not suitable. There are various milk substitutes, the most popular of which is a soy-bean preparation, although this is liable to cause diarrhoea in some infants.

Prophylactically, it is advised that infants be breast-fed from birth and occasional supplementary feeding of cow's milk should never be given. If cow's milk must be given to the infant it should be in the form of evaporated milk and not bottled milk. This is also the form in which it should be given in limited quantities if diarrhoea is present. If children who are potentially allergic are kept off cow's milk during the first few months of life they are less likely to develop major allergies subsequently.

Cow's-milk allergy may be responsible for infantile cortical hyperostosis and also sudden "cot deaths".

A. W. Frankland

79. Penicillin Allergy and Desensitization

R. E. REISMAN, N. R. ROSE, E. WITEBSKY, and C. E. ARBESMAN. *Journal of Allergy* [J. Allergy] 33, 178-187, March-April, 1962. 28 refs.

Nutrition and Metabolism

80. Aminoaciduria in Vitamin D Deficiency States in Premature Infants and Older Infants with Rickets

J. J. CHISOLM JR. and H. E. HARRISON. *Journal of Pediatrics* [J. Pediat.] 60, 206-219, Feb., 1962. 5 figs., 25 refs.

The pattern of amino-aciduria in vitamin D deficiency has been studied in 38 premature infants and in 20 older infants admitted to the Baltimore City Hospitals. The premature infants were allocated at random to one of two groups: A, the "control" group, consisted of 18 infants who received 1,500 units of vitamin D daily, while Group B was the "study" group of 20 infants who did not receive vitamin D until the age of 7 weeks; thereafter half these infants (Group B1) received 1,500 units of vitamin D daily and the other half (Group B2) received a total of 600,000 units in 6 divided doses over a 24-hour period only. No clinical signs or radiological evidence of rickets were found in Groups B1 or B2; there was some reduction in the serum calcium levels, but these returned to normal after treatment with vitamin D. There was a significant increase in amino-aciduria in Group B compared with Group A, and there was also a correlation between hypophosphataemia and amino-aciduria. These changes were reversed after treatment with vitamin D.

All the older infants, who were aged between 3 and 33 months, showed radiological evidence of rickets on admission to hospital; in 15 cases the intake of vitamin D had been deficient and in 5 the rickets resulted from intestinal malabsorption of the vitamin. Amino-aciduria of varying degree was found in 13 of the 15 infants in the first group and marked amino-aciduria in 4 of the 5 with malabsorption. Administration of prophylactic doses of vitamin D reduced or inhibited the hyperamino-aciduria even while the bone lesions remained active. The authors conclude from this study that hyperamino-aciduria is a sensitive and early index of vitamin-D deficiency and that the vitamin exerts its action on a renal tubular mechanism essential for reabsorption of all amino-acids.

R. M. Todd

81. Limitations of the I^{131} -Labeled Triolein Tests in the Diagnosis of Steatorrhea

C. G. MOERTEL, H. H. SCUDAMORE, E. E. WOLLAEGER, and C. A. OWEN JR. *Gastroenterology* [Gastroenterology] 42, 16-21, Jan., 1962. 2 figs., 22 refs.

This study was undertaken at the Mayo Clinic to determine the accuracy and sensitivity of the I^{131} -labelled triolein test as a measure of fat absorption in the diagnosis of steatorrhea. Following the oral administration of 10 to 25 μ c. of labelled triolein plus 20 g. of fat to 64 fasting subjects receiving a daily fat intake of 100 g. the urine was collected for 24 hours and the faeces for a minimum of 3 days. The proportion of the oral dose excreted in the urine and faeces was measured (and expressed as a percentage) and the faecal fat content was determined by chemical methods.

In the 28 control subjects the mean urinary excretion was 50.1% of the oral dose, whereas in the 36 patients with steatorrhea this mean was 29.7%. However, there was much overlap between the two groups, about half the

patients with steatorrhea showing urinary excretion values within the normal range, thus greatly lessening the value of the test. In regard to faecal radioactivity, this was less than 6% of the administered dose in all the normal subjects. It exceeded 6% in all patients with severe steatorrhea (that is, those excreting over 30 g. of fat in the faeces daily), but reached this level in only 10 out of 25 patients with mild steatorrhea. The authors conclude that the labelled triolein test lacks sensitivity, cannot be regarded as a reliable diagnostic aid, and by no means replaces fat intake-excretion studies.

M. Lubran

82. Diethylpropion in the Treatment of Obesity: a Cross-over Trial of a Long-acting Preparation

D. R. HADDEN and C. LUCEY. *Ulster Medical Journal* [Ulster med. J.] 30, 109-113, Dec., 1961 [received Feb. 1962]. 9 refs.

The authors describe a double-blind cross-over trial in simple obesity of a low-calorie diet and "tehuete dospan", a preparation in which diethylpropion is incorporated with a hydrophilic colloid for prolonged and sustained action. The subjects were volunteers from among patients referred to the Royal Victoria Hospital, Belfast, for obesity, and had no serious associated disease. Of the 38 who volunteered, only 22 completed the trial. The experiment continued for 2 months, and after one month there was a change-over from the drug to a placebo or vice versa.

The drug was effective in reducing weight, especially when it was given during the first month of the trial. It was considerably less effective when given after a month of treatment with a placebo. No serious side-effects were noted. It is recommended that the clinical use of this drug should be restricted to short intermittent courses.

A. G. Mullins

83. Effect of Low-calcium Diet on Urinary Calcium in Osteoporosis

S. D. BHANDARKAR and B. E. C. NORDIN. *British Medical Journal* [Brit. med. J.] 1, 145-147, Jan. 20, 1962. 2 figs., 8 refs.

At the Western Infirmary, Glasgow, urinary calcium and creatinine excretion was measured in normal subjects and patients with relatively severe osteoporosis, first while receiving the normal ward diet and then on the last 2 or 3 days of a 10-day period during which the subjects were given a diet containing less than 200 mg. of calcium daily. In the 13 normal subjects calcium excretion fell significantly during the period on the low calcium diet (from a mean of 230.6 to 167.0 mg. in 24 hours), while in the 24 osteoporotic patients the fall was insignificant (from 202.6 to 197.4 mg. per 24 hours). The ratio of calcium to creatinine excretion fell significantly in 11 of the normal subjects (from 0.24 to 0.16), but hardly changed in 17 of the osteoporotic patients (from 0.25 to 0.22). It is concluded that these findings are compatible with the view that patients with osteoporosis cannot adapt themselves to a low calcium diet by reducing urinary calcium excretion, as do normal subjects.

M. Lubran

Gastroenterology

84. Acute Gastro-intestinal Illness in General Practice

E. TUCKMAN, P. A. L. CHAPPLE, L. M. FRANKLIN, I. N. MANSER, J. T. WOODALL, K. J. RANDALL, and J. C. McDONALD. *British Medical Journal* [Brit. med. J.] 1, 135-141, Jan. 20, 1962. 3 figs., 7 refs.

A clinical, bacteriological, and epidemiological survey of acute gastro-intestinal illness is reported from a group general practice of 8,000 patients on the outskirts of South-East London. The study was carried out over the 2 years 1957 and 1958, and in all there were 738 illnesses that fell into the definition—an annual incidence of 5.2%. An epidemic of Sonne dysentery occurred in 1957, but apart from this there was a striking absence of bacterial pathogens from the 622 stool specimens examined. *Shigella sonnei* was isolated from 18% of specimens (29% in 1957 and 0.4% in 1958) and *Proteus* was found in 19% of specimens; but the significance of the latter was uncertain, because this organism was found in a similar proportion of healthy controls. A strain of E.C.H.O. virus Type 4 was isolated from only one case out of 49 tested and from none of 29 healthy children.

Clinically, the frequency of the main signs and symptoms showed few real differences between Sonne dysentery and the other illnesses. Apart from bacteriology, the best distinction was by microscopy; erythrocytes, leucocytes, and mucus were found only in cases with Sonne infections. Most of the illnesses were very mild, but Sonne dysentery caused patients to spend longer in bed. Of the 738 patients, 54 (7%) were admitted to hospital—41 with a diagnosis of appendicitis, of whom 37 were operated upon.

Patients were studied in relation to certain foods taken before onset, canteen meals, household pets, contact with similar illness, and presence of school-children in the family. The only factor that stood out clearly was the importance of schools and school-children in Sonne dysentery.

A therapeutic trial of neomycin, phthalylsulphathiazole, and kaolin was carried out on 83 patients. All these cases were bacteriologically negative. There was little difference in the 3 groups of patients, but no conclusions can be drawn from this small group of cases.

[This useful survey merely confirms that the aetiology of the great majority of the common acute gastro-intestinal illnesses is unknown and that they all follow a benign and self-limiting course. Until virological techniques improve, few advances in knowledge can be expected.] John Fry

85. Silent Peptic Ulcer: a Clinical and Pathological Study

V. M. SMITH, M. FELDMAN SR., and J. A. MEAD. *American Journal of Gastroenterology* [Amer. J. Gastroent.] 37, 55-63, Jan., 1962. 1 fig., 4 refs.

The over-all incidence of peptic ulcer is generally estimated to be about 10%, this estimate being based on the reported findings of peptic ulcer at necropsy and on the reports of radiologists. This paper from the University of Maryland, Baltimore, reports an investigation of the incidence of "silent" peptic ulcer, that is, peptic ulcer without clinical

symptoms up to the time of incidental discovery, in which radiological examination of the upper gastro-intestinal tract was carried out on three groups of subjects who had no symptoms and no history suggestive of gastro-intestinal disease:

The incidence of silent peptic ulcer, based on demonstration of an actual ulcer niche, was 7 cases (20%) in a group of 35 young male military subjects aged 18 to 22 years, 4% (one case) in a group of 25 male civilian subjects aged 29 to 56 years, and 4% (one case) in a group of 25 female nurses aged 18 to 22 years. The incidence in this series of 85 persons was thus 10.6%. A "duodenal abnormality without niche", suggestive of possible duodenal ulcer, was demonstrated in an additional 10% of the military group and in an additional 4% of the male civilian group and of the female group.

A retrospective study was then made of the records of 84 consecutive patients who had been found at necropsy to have chronic peptic ulcer of the stomach or duodenum, or of both. This showed that in 47.6% there had been a long history of symptoms of peptic ulcer, in 8.3% symptoms of peptic ulcer for less than 60 days and in 4.8% less than 10 days before the discovery of the ulcer, while in the remaining 33 cases (39.3%) there were no symptoms before discovery of peptic ulcer consequent on the occurrence of acute haemorrhage, perforation, abdominal operation for other cause, or death. Haemorrhage, perforation, or both, had occurred in 76% of the "silent" group, and in 71% of the symptomatic group and caused or largely contributed to the fatal outcome in these cases. The relative frequency of gastric, duodenal, and combined gastric and duodenal ulcers was similar in both groups.

In view of these findings the authors recommend a more intensive effort by clinicians to detect cases of silent peptic ulcer. Also recommended is the routine use of the "string test" as a screening test, followed by radiological examination of patients in whom the string shows gross blood deposits.

Joseph Parness

86. Aspirin and Chronic Gastric Ulcer

R. A. DOUGLAS and E. D. JOHNSTON. *Medical Journal of Australia* [Med. J. Aust.] 2, 893-897, Dec. 2, 1961. 8 refs.

A total of 77 patients with chronic gastric ulcer were admitted to the General Hospital, Townsville, Queensland, between July, 1956, and December, 1959, and questioned about their aspirin intake. Of these, only 14 (12 males) did not take aspirin. The average yearly intake in tablets or powders was 1,460 units, mainly for chronic headache. The population of Townsville and surrounding area, estimated at 100,000, consumed 12.8 million units a year. On the assumption that approximately 60,000 of that population took aspirin the average yearly consumption was 210 units. A questionnaire about aspirin consumption was sent to 200 people whose names were taken at random from the electoral roll; only 99 replied and their average intake was 320 units a year. A similar questionnaire was sent to 77 patients who had been treated in the hospital for duodenal ulcer; the

average intake of aspirin of the 36 who replied was 232 units.

The authors conclude that aspirin bears a causal relationship to gastric ulcer in at least 50% of patients, and suggest that the triad of chronic headache, aspirin taking, and gastric ulcer constitutes an important clinical syndrome.

Arnold Pines

87. Inadequacy of the Medical History in the Diagnosis of Duodenal Ulcer

J. P. DUNN and L. E. ETTER. *New England Journal of Medicine* [New Engl. J. Med.] 266, 68-72, Jan. 11, 1962. 13 refs.

Since 1957, the University of Pittsburgh has provided facilities for the routine medical examination each year of the management personnel of local firms. The present authors have made a comparative study of the dyspeptic history given by 206 consecutive individuals and the interpretation of radiographs of the upper gastro-intestinal tract in these same individuals. They found radiological evidence of duodenal ulcer in 49% of those with a "negative" clinical history.

B. F. Swynnerton

88. The Association of Auto-immune Thyroiditis and Cirrhosis of the Liver

W. W. BUCHANAN, J. CROOKS, D. A. KOUTRAS, A. G. MEL-ROSE and R. B. GOUDIE. *Scottish Medical Journal* [Scot. med. J.] 7, 22-26, Jan., 1962. 35 refs.

The authors, at the Western Infirmary and the Southern General Hospital, Glasgow, have investigated the possible relationship between autoimmune or Hashimoto's thyroiditis and cirrhosis of the liver. Of 30 patients (16 females and 14 males) with cirrhosis of the liver, 5 females were found to have a positive precipitin or complement-fixation reaction for thyroid autoantibodies. Only one male patient gave a thyroid-specific complement-fixation reaction. The mean protein-bound iodine level in the female cirrhotic patients was not significantly different from the mean of a series of healthy controls.

In addition, 41 patients with autoimmune thyroiditis were screened for stigmata of liver disease and "bromsulphalein" tests were carried out. However, only 6 of the 41 patients had abnormal bromsulphalein retention, exceeding 6% at 45 minutes. Of the 6 patients, one had hepatosplenomegaly, but liver biopsy showed no evidence of cirrhosis, and the remaining 5 patients had normal liver histology.

The finding of thyroid autoantibodies in a high proportion of middle-aged females with cirrhosis of the liver suggests that autoimmune mechanisms may be involved in the production of cirrhosis of the liver.

I. McLean Baird

89. Hepatic Photoscintigraphy by the Technique of Colloidal Radioactive Gold. (La photoscintigraphie hépatique par la technique de l'or colloïdal radioactif)

R. FAUVERT and A. LOVERDO. *Archives des maladies de l'appareil digestif et des maladies de la nutrition* [Arch. Mal. Appar. dig.] 51, 43-54, Jan.-Feb., 1962. 11 figs., 9 refs.

The value of the technique of hepatic photoscintigraphy is described by the authors, who have used it at the Hôpital Beaujon, Paris. The technique consists in the administration of radioactive colloidal gold, which is largely removed by the Kupffer cells of the liver. The activity of this substance in the liver can be "mapped" by means of a scintilla-

tion counter and regional differences detected and graphically represented.

The special indications for this technique are for the accurate determination of liver size and for the detection of hepatic cysts and abscesses. Hepatic cancer, both primary and secondary, may also be detected by this method of investigation, the map of the activity in the liver in each case showing "silent" areas corresponding to the presence of localized liver destruction by the neoplasm.

A. E. Read

90. Diagnostic Value of Hepatic Scintillography—a Critical Study. (Valeur diagnostique de la scintillographie hépatique. Étude critique)

J. CAROLI and B. BONNEVILLE. *Archives des maladies de l'appareil digestif et des maladies de la nutrition* [Arch. Mal. Appar. dig.] 51, 55-82, Jan.-Feb., 1962. 26 figs., 7 refs.

The authors discuss the diagnostic value of the technique of hepatic scintillography as applied to 274 patients with liver disease. In the majority of examinations labelled radioactive rose bengal was used, for the authors point out that errors are likely to occur if serial scintillograms are not obtained. Excretion of rose bengal in the biliary tract and intestines may result in a changing pattern, and serial examinations will detect this excretion and avoid attaching undue importance to the pseudolacunae created by such intestinal excretion.

The pitfalls due to anatomical variations in morphology of the normal liver are emphasized and the importance of careful clinical palpation before scintillographic examination is stressed; this is particularly important when space-occupying lesions of the liver are present. Such conditions as amyloid infiltration and haemochromatosis merely give a picture of hepatomegaly with uniform activity. The authors compare the usefulness of this technique with peritoneoscopy and point out that the advantages of scintillography lie in the detection of lesions within the liver substance which may not be visible on peritoneoscopy. Labelled rose bengal is a suitable radioactive material to use except when liver cell function is impaired or there is jaundice; in these circumstances uptake of this substance may not then be satisfactory and colloidal gold is then to be preferred.

A. E. Read

91. Newer Methods for Localization of Obscure Small-bowel Bleeding

R. P. PILLOW, L. D. HILL, P. A. RAGEN, J. S. SIEMSEN, and L. A. WALKER. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 23-26, Jan. 6, 1962. 1 fig., 11 refs.

The site of bleeding in the small intestine is sometimes difficult to detect by conventional radiological procedures. The authors describe a technique they have found useful in which the patient's own erythrocytes are labelled with radioactive chromium and then re-injected. Later the tagged cells may be recovered by means of a Miller-Abbott tube, through which intestinal contents are aspirated at various levels.

A. Gordon Beckett

92. Suppurative Pylephlebitis with Multiple Liver Abscesses Complicating Regional Ileitis: Review of Literature—1940-1960

B. LERMAN, J. H. GARLOCK, and H. D. JANOWITZ. *Annals of Surgery* [Ann. Surg.] 155, 441-448, March, 1962. 2 figs., 36 refs.

Cardiovascular System

93. Iodide Retention in Cardiac Disease

G. L. SEARLE, W. A. REILLY, and K. G. SCOTT. *Metabolism: Clinical and Experimental [Metabolism]* 10, 848-851, Nov., 1961. 5 refs.

Twelve compensated and 12 decompensated cardiac patients and a control group of 49 euthyroid hospital patients received 100 μ c. of I^{131} orally. Iodide retention in plasma was significantly greater in the cardiac patients than in the control group; however, neither I^{131} thyroid uptake nor conversion of I^{131} to protein-bound I^{131} was significantly affected.—[Authors' summary.]

94. Alterations in Blood Volume during "Normovolemic" Total Body Perfusion

R. S. LITWAK, A. J. GILSON, R. SLONIM, C. C. McCUNE, I. KIEM, and H. L. GADBOYS. *Journal of Thoracic and Cardiovascular Surgery [J. thorac. cardiovasc. Surg.]* 42, 477-488, Oct., 1961. 9 figs., 7 refs.

The authors have found that in spite of the most careful estimation of blood loss and its quantitative replacement during cardiopulmonary by-pass, most of their patients have hitherto shown a considerable postoperative blood volume deficit, the average figure being 15.4 ml. per kg. body weight. In the present study of 36 patients undergoing open heart surgery at the Jackson Memorial Hospital, Miami, the preoperative blood volume was determined by means of labelled albumin and/or labelled erythrocytes, while blood loss during operation was measured in the usual way by the weighing of swabs and recording of amounts of blood taken for such purposes as laboratory studies and priming of the circuit. At the end of the operation the blood balance was kept on the positive side by the infusion of 6 ml. of blood per kg. body weight to cover unmeasured loss into the mediastinum and pleural cavities, and the patients were weighed on a metabolic scale. Finally, 2 hours after operation the blood volume was again estimated using radioactive isotopes. In spite of these assiduous efforts it was found that 32 of the 36 patients were suffering from a blood volume deficit and, in the authors' opinion, this hypovolaemia was a major factor in the death of 4 patients. Deficits were noticeably frequent and often large in cases in which a left-to-right cardiac shunt had been corrected.

The breakdown of the figures from this study reveals that there is no satisfactory or reliable guide to the maintenance of a normal blood volume during and after perfusion. Pre- and postoperative weighing is known to be misleading and the recording of venous and arterial pressures, although helpful clinically, does not necessarily reveal even major blood loss. The authors suggest, however, that there may be some significant relation between blood volume loss and such measurements when both venous and arterial pressures rise during perfusion. But even when it is so arranged that patients automatically control their own blood volume during perfusion by the use of a predicted and constant flow-rate, major postoperative blood volume deficits have been shown still to occur. The authors conclude that there

is as yet no predictable means of maintaining normovolaemia during and after by-pass and that until this is devised hypovolaemia will continue to be a major factor in the survival or death of patients undergoing this type of surgery.

A. M. Macarthur

95. An Appraisal of Clinical Results in Open Mitral Valvuloplasty

J. D. MORRIS, H. SLOAN, W. S. WILSON, and R. L. BRANDT. *Journal of Thoracic and Cardiovascular Surgery [J. thorac. cardiovasc. Surg.]* 43, 17-37, Jan., 1962. 12 figs., 13 refs.

The authors recount from the University of Michigan Medical Center, Ann Arbor, their experience with 42 open-heart operations on the mitral valve—for stenosis in 12 cases, pure mitral insufficiency in 16, and mixed lesions in 14. There were 5 deaths, 4 of these being in patients who were bad risks. In dealing with mitral stenosis they have no intention of advocating open operation in all cases of this lesion, but the results of such operations nevertheless were satisfactory. The approach was through a right thoracotomy under hypothermia obtained by external cooling augmented by perfusion with a blood heat exchange to 30° C. Once perfusion had been started the left atrium was opened with care to avoid frothing and air embolus. They describe their method of performing valvotomy and, in the case of mitral insufficiency, a type of plastic operation which was carried out at the end of each commissure so as to narrow the valve and, by adding a short length of prosthesis, to enable inadequate cusps to come together.

The result of surgery for valvular stenosis was very good and a number of cases of mitral insufficiency did well. It should be noted that of the 16 cases, 11 were classed as of congenital origin (average age of patient 4 years). Complicated cases required nearly a year to develop maximum ultimate improvement.

T. Holmes Sellors

96. Failure of Propatyl Nitrate and Pentaerythritol Tetranitrate to Prevent Attacks of Angina Pectoris

S. ORAM and E. SÖWTON. *British Medical Journal [Brit. med. J.]* 2, 1745-1746, Dec., 30, 1961. 12 refs.

The authors report from King's College Hospital, London, the results of a double-blind controlled clinical trial of propatyl nitrate ("gina") and pentaerythritol tetranitrate ("mycardol") in the prevention of attacks of angina pectoris. In the doses used, 10 and 30 mg. respectively given sublingually, the two drugs did not differ significantly from a placebo in abolishing or diminishing the frequency of attacks of anginal pain.

A. I. Suchett-Kaye

97. The Relationship between Coronary Heart Disease and the Presence of Certain Physical Characteristics

H. Z. POMERANTZ. *Canadian Medical Association Journal [Canad. med. Ass. J.]* 86, 57-60, Jan. 13, 1962. 14 refs.

This is the report of a study undertaken at the Reddy Memorial Hospital, Montreal, to ascertain how frequently certain physical traits, such as arcus senilis, greying of hair, and large wrists occur in patients with coronary heart disease.

The study group consisted of 52 men and 14 women with clinical and electrocardiographic evidence of myocardial infarction. The control group of 43 men and 12 women were free from coronary arterial disease and had attended for a routine "check-up". Statistical analysis of the data revealed that arcus senilis before the age of 56 and large wrists (over 8 inches (20.3 cm.) circumference) were frequent in the group with coronary heart disease (statistical significance at the 5% level). The occurrence of moderate greying and of premature greying was found to be highly significant (at the 1% level).

The author claims that the present study confirms the validity of long-standing clinical impressions about physical make-up and coronary disease.

A. I. Suchett-Kaye

DIAGNOSTIC METHODS

98. Radioelectrocardiography during Exercise in Patients with Angina Pectoris. Comparison with the Postexercise Electrocardiogram

S. BELLET, M. ELIAKIM, S. DELIYIANNIS, and D. LAVAN. *Circulation [Circulation]* 25, 5-14, Jan., 1962. 6 figs., 37 refs.

In radioelectrocardiography two electrodes are attached firmly to the skin on either side of the chest in the 5th intercostal space connected to a small radio transmitter carried in the patient's pocket, and the electrocardiogram so broadcast is picked up by a receiver from which it is relayed to a conventional electrocardiograph or oscilloscope. The absence of wire connexions and of interference due to muscle potentials permit records to be obtained while the patient is undergoing exercise. In this investigation reported from the Philadelphia General Hospital (University of Pennsylvania) a group of 70 patients, all with anginal symptoms and 8 having suffered previous myocardial infarction, were studied. A complete 12-lead electrocardiogram (ECG) was taken at rest in the recumbent position with a conventional electrocardiograph and the patient was then attached to the radio transmitter, tracings being taken in both recumbent and upright positions. A single Master two-step test was then performed and the ECG recorded continually. Records were also taken at 2 to 8 seconds after completing the exercise as well as at 1, 3, 5, and 8 minutes thereafter.

On the basis of a previous study of 127 normal individuals undergoing a double Master two-step test the following changes were considered to be definite criteria of abnormality: (1) Appearance or increase in an ischaemic S-T segment depression of 1 mm. or more. (2) Appearance or increase in S-T segment elevation of 1 mm. or more. (3) T-wave inversion or the reversion of a negative T wave to an upright position. (4) Frank inversion of the U wave. (5) Widening or narrowing of a previously widened QRS complex. (6) Appearance of coupling or runs of premature beats. The following changes were considered probably to be abnormal: (1) Ischaemic S-T depression or T-wave inversion in occasional cycles. (2) Marked changes in contour or biphasic T waves. (3) Appearance of prominent U waves. (4) Appearance of at least three premature beats in an isolated finding.

Of the 70 patients, 23 had a normal resting ECG, but 11 (48%) of these showed abnormal changes (in 6 cases definite and in 5 probable) during exercise, and 6 (26%) showed

similar changes (in 4 definite and in 2 probable) in the post-exercise period. In this group 5 patients showed abnormal changes only during exercise and none had changes limited to the post-exercise period. Among the remaining 47 patients with abnormal resting ECGs 26 (55%) showed abnormal changes during exercise and 18 (38%) in the post-exercise period, while 8 patients showed abnormal changes only during exercise; in 4 others, although abnormal changes were recorded in the immediate post-exercise period (2 to 8 seconds), these had disappeared one minute after exercise. Thus it was shown that in 17 of the 37 patients with an abnormal response the changes were linked to the period of exercise or the immediate post-exercise period. The authors conclude that in performing this test for the diagnosis of myocardial ischaemia ECGs should be recorded both during and after exercise.

Eirian Williams

99. Transseptal Left Heart Catheterization. A Review of 450 Studies and Description of an Improved Technique

E. C. BROCKENBROUGH, E. BRAUNWALD, and J. ROSS JR. *Circulation [Circulation]* 25, 15-21, Jan., 1962. 4 figs., 16 refs.

Transseptal left heart catheterization was first performed in experimental animals by puncturing the intact interatrial septum with a needle passed into the right atrium through a catheter introduced into a femoral vein. In man a specially constructed needle of small calibre (No. 19 gauge) was at first employed and subsequently in order to measure left ventricular pressure a similar needle of larger calibre (No. 17 gauge) through which a fine plastic catheter could be passed was used. Transseptal left heart catheterization by this technique has been performed on 294 occasions at the National Heart Institute, Bethesda, Maryland, without fatality. The aorta was punctured in 3 patients, of whom one suffered chest pain for several days following catheterization and developed a small pleural effusion, another required pericardiocentesis and transfusion, but the 3rd recovered without symptoms. Blind left ventricular catheterization was achieved in about 75% of cases, but was sometimes impossible in the presence of pure mitral regurgitation or mixed mitral valve lesions. This technique was not consistently satisfactory when angiocardiograms were attempted from the left atrium and furthermore selective left ventricular injections of dye could not be made. Ligation of the saphenous vein after the procedure also limited the number of studies possible in each patient.

In this paper the authors describe a method of percutaneous transseptal left heart catheterization in which a specially constructed catheter is introduced into the femoral vein by the Seldinger technique. The distal end of the catheter is curved in order to facilitate its passage into the left ventricle, although it is straightened by means of a stylet during its passage through the inferior vena cava. With the catheter in the right atrium the stylet is withdrawn and replaced by a transseptal needle, and after the septum has been punctured the catheter is slipped over the needle into the left atrium and thence into the left ventricle. Out of 156 such studies the left atrium was successfully entered in all but 2 patients and the left ventricle was catheterized in 143 of the 151 studies in which this was attempted. Left heart angiography was carried out on 33 patients, in 22 the injection being made into the ventricle and in 11 into the atrium. There were no deaths in this series and no instance of aortic

puncture or cardiac tamponade. Small amounts of blood were found in the pericardial spaces of several patients operated upon subsequently and this was attributed to puncture of the free wall of the right atrium. Two patients developed transient atrial fibrillation and 2 transient hypotension. The authors stress the many advantages of this modification of the technique of left heart catheterization.

Eirian Williams

100. Electrocardiographic Patterns in Patients with Cerebrovascular Accidents

V. FENTZ and J. GORMSEN. *Circulation* [Circulation] 25, 22-28, Jan., 1962. 3 figs., 10 refs.

At the Copenhagen County Hospital, Hellerup, Denmark, electrocardiograms (ECGs) were recorded soon after admission and again later in 69 patients with cerebral infarction and in 21 with intracranial haemorrhage, which was intracerebral in 16 and subarachnoid in 5. The clinical diagnosis of cerebral infarction was supported in most cases by the findings on carotid arteriography. In 39 of the 69 patients with cerebral infarction the ECG was normal, in 19 it was abnormal owing to cardiac infarction or hypertension, while in 11 (15%) ECG changes were present which were not attributable to heart disease. In 4 of the patients with intracranial haemorrhage the ECG was normal, in 2 it showed changes due to heart disease, and in 15 (71%), 2 with subarachnoid haemorrhage and 13 with intracerebral haemorrhage, changes were present which could not be attributed to heart disease. The abnormalities noted were transient S-T segment depression, T-wave inversion and prolongation of QT_c beyond 0.45 second; the S-T and T-wave changes closely simulated those of ischaemic heart disease.

The authors conclude that in patients with cerebrovascular accidents a particularly critical assessment should be made of any changes present in the electrocardiogram.

Eirian Williams

CONGENITAL HEART DISEASE

101. Atrial Septal Defects of the Secundum Type

R. E. GROSS. *Progress in Cardiovascular Diseases* [Progr. cardiovasc. Dis.] 4, 301-311, Jan., 1962. 17 refs.

Among the commoner forms of congenital cardiac abnormality atrial septal defect of secundum type is more frequently encountered in females and may produce little or no symptoms in early life unless the defect is large with a big left-to-right interatrial shunt. Apart from the heavier work load upon the right heart the main hazard of an open septum is the tendency to a progressive increase in the pulmonary vascular resistance, leading to reversal of blood flow, cyanosis, and death. Ideally surgical closure should be advised in childhood or adolescence when the right ventricular output is shown to be raised 50% over that of the left heart. Although the technical difficulties are no greater in adults, the longer period of heart strain and consequent possible pulmonary vascular changes often mean that older patients require more prolonged medical care. The diagnosis is suggested by the presence of right cardiac enlargement, a powerful apical "thrust", a systolic murmur and perhaps a thrill maximal over the second and third left interspaces, and a wide splitting of the second heart sound; also the finding in the electrocardiogram of right axis deviation,

a complete or incomplete right bundle-branch block, a large P wave, a widened, notched QRS complex, and a prolonged P-R interval. The diagnosis is confirmed by cardiac catheterization, which permits an accurate measurement of the blood flow and indicates anomalous venous drainage and changes in the pulmonary vascular resistance.

After tracing the history of various operative procedures designed to effect closure in these cases the author describes his own method. This includes a pump oxygenator, normothermia, extracorporeal circulation with cardiopulmonary by-pass, and approach to the defect through the right atrium. Since 1957, in 166 patients, including 28 with anomalous venous return, effective closure of the defect has been obtained by this method. The great majority of defects of this type can be closed in the relaxed heart by direct suture, but in those cases in which the anterior or antero-inferior margins of the orifice prove friable a compressed "ivalon" sponge on-lay graft should be used. It is also emphasized that anomalous veins must be sought and suture so devised as to divert their orifices back into the left atrium. In uncomplicated cases the mortality is low—in this series 3.6%. Of these 6 patients, one died from massive haemorrhage 10 days after operation and in 3 others there was associated but unsuspected mitral stenosis which proved fatal when the atrial septal defect was closed. It is therefore urged that in all such cases the mitral valve should be explored at operation even though no mitral symptoms have been present.

C. A. Jackson

102. The Surgical Treatment of Ventricular Septal Defect: an Analysis of 300 Consecutive Surgical Cases

D. A. COOLEY, H. E. GARRETT, and H. S. HOWARD. *Progress in Cardiovascular Diseases* [Progr. cardiovasc. Dis.] 4, 312-323, Jan., 1962. 7 figs., 7 refs.

During the period January, 1956, to January, 1961, at the Children's and Methodist Hospitals, Houston, Texas, the use of cardiopulmonary by-pass with a bubble pump oxygenator has permitted the surgical treatment of 1,044 patients with cardiac lesions. Of these patients, 300 had interventricular septal defect, which in 59 cases was associated with other congenital lesions. The septal defects were arbitrarily classified according to anatomical location into four types, as follows. Type 1 (14 cases) represented a high defect above the crista supraventricularis. Type 2 (238 cases) involved the membranous septum. Defects of Type 3 (11 cases) were located under the posterior leaflet of the tricuspid valve close to the tricuspid annulus. Type 4 (9 cases) involved the inferior portion of the muscular septum. There were in addition 15 patients with ventricular-atrial defects, 6 with multiple ventricular defects, and 4 with a "common ventricle". In 46% of the patients the defect could be repaired by direct suture, while 54% required a patch prosthesis of knitted "dacron".

In infants under 2 years of age mortality was high (0 to 1 year 43% and 1 to 2 years 28.6%), but some of these patients could be salvaged by a temporary primary procedure of pulmonary arterial banding, with radical repair at a later age. The most favourable surgical results were obtained in the age group 2 to 14 years (14 deaths among 193 cases, a mortality of 7.3%), while in the 3 patients aged over 40 years in the series the defect was corrected successfully. Omitting the infants under 2 years of age, many of whom could not in any case have survived, the mortality in the remaining 256 cases was 9%. The significant feature in

prognosis was the severity of pulmonary hypertension and the direction of the intracardiac shunt, the former being expressed as a ratio of pulmonary arterial pressure. A femoral:pulmonary artery pressure ratio of less than 0.50 and not greater than 0.85 was a favourable feature, but ratios higher than this and associated with a right-to-left shunt proved most hazardous. With increasing experience of perfusion technique, careful selection of cases, and strict postoperative care it is considered that it should be possible to achieve an operative mortality of less than 5%. It is concluded that pulmonary hypertension remains the greatest single cause of operative failure in these cases; heart block, at one time greatly feared, has been eliminated by performing careful suture of the slowly contracting heart, while postoperative haemorrhage has been mastered by early recognition and re-operation as required.

C. A. Jackson

103. Congenital Aortic Stenosis. Operative Indications and Surgical Results

M. H. LEES, A. J. HAUCK, G. W. B. STARKEY, A. S. NADAS, and R. E. GROSS. *British Heart Journal* [Brit. Heart J.] 24, 31-38, Jan., 1962. 2 figs., 23 refs.

At the Children's Hospital, Boston, during the period 1957-60, 42 patients aged 6 weeks to 20 years with congenital aortic stenosis were operated on by the transaortic approach and with the aid of total cardiopulmonary by-pass and potassium citrate cardioplegia. About half of these patients were subjected to left heart catheterization on the criteria that those with symptoms or with electrocardiographic evidence of left ventricular strain are at risk of sudden death. Operation was advised if the peak systolic gradient across the valve exceeded 20 mm. Hg, the mean ejection gradient was 30 mm., or if the calculated valve area was less than 0.5 sq. cm.; at operation all such patients were found to have severe stenosis. In 26 cases there was isolated valvular stenosis, in 11 subvalvular stenosis, and in 5 complicated lesions such as aortic hypoplasia or coarctation.

Of the 42 patients, 6 died, a mortality of 14%. Most of the survivors had relief of symptoms. Cardiac enlargement, which was seldom severe, was unaffected. Aortic regurgitation, which was present in all the subvalvular cases before operation but was not significant, was sometimes improved. Insignificant regurgitation followed operation in 5 cases. In cases of isolated valvular stenosis the electrocardiogram nearly always improved, sometimes to normal, but in the subvalvular cases there was seldom any change. Cardiac catheterization, repeated in 13 cases, usually showed an improvement in the peak gradient, with in some cases its abolition. The prognosis after operation for valvular stenosis appears to be good, but is less favourable for subvalvular stenosis. When this diagnosis can be made, obstruction is seldom mild, and early operation is advised.

M. Meredith Brown

104. Thrombocytopenia in Congenital Heart Disease

D. VEREL, S. J. MAZURKIE, E. K. BLACKBURN, J. L. EMERY, S. VARADI, and L. WOLMAN. *British Heart Journal* [Brit. Heart J.] 24, 92-94, Jan., 1962. 7 refs.

Idiopathic thrombocytopenic purpura was found in 4% of a group of patients with cyanotic congenital heart disease and in one uncyanosed patient. The importance of this finding in relation to cardiac surgery and the risk of cerebral vascular accidents is emphasized.—[Authors' summary.]

PERICARDIUM

105. Inspiratory Traction on the Pericardium: the Cause of Pulsus Paradoxus in Pericardial Disease

W. DOCK. *Archives of Internal Medicine* [Arch. intern. Med.] 108, 837-840, Dec., 1961. 1 fig., 8 refs.

This paper from the State University of New York, Downstate Medical Center, discusses the cause of paradoxical pulsation in connexion with diseases of the pericardium. The author, in a study of 6 cadavers with normal pericardial sacs, has simulated respiratory movements of the diaphragm and sternum. When the pressure in the pericardial sac was raised by the infusion of water it was found that traction on the diaphragm caused a significant further rise in pressure, this rise being significantly greater than that produced by elevation of the sternum. The increase in pressure was proportional to the initial pressure in the pericardial sac.

The author concludes that the inspiratory descent of the diaphragm is the cardinal factor in decreasing the diastolic volume of the heart in patients with pericardial disease, and that this explains the rise in venous pressure during inspiration. He defines paradoxical pulse as an inspiratory decrease in arterial pressure without the inspiratory fall in venous pressure normally seen. J. Warwick Buckler

106. Acute Benign Pericarditis: Virologic Study of 34 Patients

R. T. JOHNSON, B. PORTNOY, N. G. ROGERS, and E. L. BUESCHER. *Archives of Internal Medicine* [Arch. intern. Med.] 108, 823-832, Dec., 1961. Bibliography.

This paper from the Walter Reed Army Institute of Research, Washington, D.C., gives details of 34 male patients with a diagnosis of acute benign pericarditis. Although the authors saw none of these patients, full clinical data were available. The criteria for diagnosis were: (1) an acute illness with severe pain of cardiac type; (2) pericardial friction and/or electrocardiographic changes consistent with pericarditis; and (3) a history and subsequent course not diagnostic of any other cause of pericarditis.

Two samples of serum were taken from each patient, the first before the 10th day of illness and the second after the 14th day. Stool and throat washings from 12 of the patients were also examined, and pericardial fluid from one patient. Serological tests were made for Group-B Coxsackie virus Types 1 to 5; influenza virus Types A, A1, A2 (Asian), and B; haemadsorption virus Types I and II (para III and I); mumps virus; adenovirus group; psittacosis-lymphogranuloma venereum group of viruses; Q-fever rickettsia; primary atypical pneumonia; and infectious mononucleosis. In addition, reactions suggestive of infectious mononucleosis and primary atypical pneumonia were studied further, and evidence for infection with E.C.H.O. virus Types 8 and 9, lymphocytic choriomeningitis virus, and the rickettsiae of spotted fever and typhus was also looked for where indicated. For virus isolation, specimens were inoculated into suckling mice and into monkey kidney and cell cultures. Throat washings were inoculated into amniotic sacs.

The clinical findings are briefly outlined together with the electrocardiographic changes and x-ray findings. A leucocytosis greater than 10,000 per c.mm. was found in 20 of the patients; the other findings conform to those of other reported studies. In 29 of the 34 patients no aetiological

viral infection was found, and in the remaining 5 patients the following specific infections occurred during the time when the patient had pericarditis: Group-B Coxsackie virus, E.C.H.O. virus Type 8, mumps and infectious mononucleosis, and in one case a rather doubtful respiratory adenovirus.

The authors therefore conclude that their careful search for aetiological agents shows that no single virus can be incriminated as the cause of sporadic acute benign pericarditis. The specific infections which were found in 5 of the patients were coincidental and therefore not necessarily aetiological. They consider that their techniques were satisfactory, as evidenced by their previous experience in other viral diseases. They suggest that agents other than viruses may be responsible for the syndrome, or that mechanisms other than actual infection of the pericardium may cause the disease. The various post-infectious and allergic types of reaction associated with pericarditis should always be considered, and acute benign pericarditis should be regarded as having a diverse aetiology.

J. Warwick Buckler

MYOCARDIUM

107. Endomyocardial Fibrosis of the Right Ventricle. D. G. ABRAHAM. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 1-20, Jan., 1962. 14 figs., bibliography.

This communication, like the author's previous papers (*Lancet*, 1959, 2, 111, and *Quart. J. Med.*, 1960, 29, 629) which described left ventricular endomyocardial fibrosis, comes from University College, Ibadan, Nigeria. The disease, of obscure aetiology, is rare in all parts of the world except certain African territories, where it is one of the commoner causes of cardiac disability. In some patients there is no evidence of left ventricular involvement when first seen, the signs being entirely those of severe right ventricular disease. In the majority of such patients there is an initial illness characterized by malaise, fever, and generalized swelling. After a few weeks the swelling of legs and face disappears, but that of the abdomen remains. In a minority, however, the initial illness passes into a state of "chronic activity" with low-grade fever, anaemia, a raised erythrocyte sedimentation rate, malaise, and anorexia. Swelling of the legs persists, accompanied by pleural and pericardial effusions and a very high venous blood pressure. This state may "smoulder" for months or a year or two, either merging into the chronic inactive form or terminating in death.

The majority of patients in the chronic inactive state show the following typical features: a very high venous pressure with systolic expansion of neck veins, massive ascites, and complete lack of dependent oedema; the arterial pulse is small and may be paradoxical; atrial fibrillation may be present; when ascitic fluid is drained the liver is always found to be large and is frequently pulsatile. Radiologically, the heart shadow is large and globular with strikingly clear lung fields. Calcification may be seen within the cardiac shadow in the region of the outflow tract of the right ventricle.

Electrocardiography and cardiac catheterization have not proved to be of use in diagnosis, but angiocardigraphic studies have added to our knowledge of the disease. In particular, the size of the right atrium, presence or absence

of pericardial effusion, and shrinkage of the right ventricular cavity are well demonstrated. Retrograde filling of the azygos vein was found on several occasions. Morbid anatomical studies show that the fibrotic process starts at the apex of the right ventricle and extends along both inflow and outflow tracts. The papillary muscles, chordae, and even the leaflets of the tricuspid valve may be incorporated in the fibrotic process. The valve is thus grossly incompetent and aneurysmal dilatation of the right atrium results. The fibrotic process also affects the endocardium of the outflow tract, stopping short of the pulmonary valve. It is in this area that calcification so frequently occurs. As fibrosis extends, mural thrombosis occurs and leads to further obliteration of the ventricular cavity. The whole right heart comes to approximate to a single atrioventricular chamber with the atrium predominant.

In diagnosis, constrictive pericarditis bears some resemblance, but the size of the heart and the presence of tricuspid incompetence are usually distinctive. The character of the jugular pulsation also serves to distinguish pericardial effusion. Cardiomyopathy is associated with marked dyspnoea and dependent oedema. Haemodynamic studies have shown that patients with chronic endomyocardial fibrosis of the right ventricle are not necessarily in congestive cardiac failure, for the cardiac output is shown to rise with effort, thus explaining the absence of dependent oedema. Although liver biopsy examination and liver function tests suggest that liver structure and function are severely deranged, the author shows that ascites in this condition is unlikely to be hepatic in origin. It is suggested that it is a compensatory mechanism to maintain the high venous pressure and cardiac output, for removal of the ascitic fluid results in a marked fall in venous pressure. Arterial oxygen desaturation and clubbing of fingers may be related to direct shunting of azygos venous blood to the pulmonary veins owing to the high central venous pressure. T. Semple

HYPERTENSION

108. Arterial Pressure in Young People. (Об артериальном давлении у лиц молодого возраста) P. V. SPIRINA. *Советская Медицина* [Sovetsk. Med.] 25, 55-58, Jan., 1962. 8 refs.

Many authors have studied the question of arterial blood pressure in young persons, but have come to almost as many different conclusions. Gelman in 1927 reported that 8% of males and 2% of females under the age of 20 had raised arterial pressure, while during the war figures of 13.2% and 11.7% respectively were reported. But what precisely constitutes a raised blood pressure is still a matter of divergent opinion. The present author has therefore determined the blood pressure in 1,706 pupils and students between 12 and 20 years of age and presents her results in a series of tables. These show that (1) among pupils aged 12 to 14 the mean maximum systolic pressure was 114.5 mm. Hg, with a range of 106.6 to 121.4 mm. Hg. In those aged 15 to 17 years it was 116.5 (range 109.6 to 123.4) mm. Hg, while in those aged 18 to 20 it was 116.5 (range 108.5 to 124.5) mm. Hg. (2) The mean diastolic pressures in the three age groups respectively were 70.7 (range 64.6 to 76.8) mm. Hg, 71.1 (range 64.8 to 77.4) mm. Hg, and 76.8 (range 69.6 to 84.2) mm. Hg. Out of 1,476 pupils, all from ordin-

ary schools, only 28 (1.9%) showed a raised arterial pressure. The remaining 230 were from special schools (for the blind or deaf and dumb) and were of the same age, but none of them had a raised blood pressure. *H. W. Swann*

109. Capillary Resistance to Suction in Hypertension

K. R. GOUGH. *British Medical Journal* [Brit. med. J.] 1, 21-24, Jan. 6, 1962. 4 figs., 21 refs.

The author of this paper from the Bristol Royal Infirmary has studied the resistance of the capillaries to suction in 234 hypertensive patients and 280 healthy controls, the groups containing equal numbers of each sex. The method consisted in the application of a measured amount of negative pressure by means of a suction chamber to the skin of the interscapular area of the back for 30 seconds. This area of skin was chosen because its properties are constant over a wide area, permitting a large number of determinations at one time. Estimations were repeated at varying levels of negative pressure until one was found which produced only 1 to 3 petechiae at 30 seconds, and the pressure at this point was taken as the capillary "resistance".

In normal subjects there was a well-marked decline in capillary resistance with increasing age. No significant difference between the sexes was observed, and the results were reproducible from day to day, or at different times of the day in the same subject. The progressive fall in capillary resistance with age is attributed to loss of support for the vessels from the surrounding connective tissue.

The hypertensive patients were divided into three groups according to the retinal changes. In those with arterial changes only capillary resistance did not differ from that in healthy controls of the same age. Patients with haemorrhages or exudates in the retinae, however, and especially those with papilloedema, had significantly lower levels of capillary resistance at all ages. This diminished capillary resistance in the more severe grades of hypertension was not directly related to the height of the diastolic pressure, since it did not occur with an equally high diastolic pressure in many of the patients in the more benign group. It is suggested that some generalized functional change in the small blood vessels may occur when hypertension passes from the benign to the malignant phase. *M. Harington*

110. Pharmacodynamics and Clinical Use of Guanethidine, Bretylium and "Methyldopa"

W. M. KIRKENDALL and W. R. WILSON. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 107-115, Jan., 1962. 5 figs., 26 refs.

The authors of this paper from the State University of Iowa College of Medicine, describe their clinical experience with guanethidine, bretylium, and "methyldopa" in the treatment of hypertension and discuss the pharmacology of these drugs. More than 70 patients were treated with guanethidine. During the first 2 months they required an average of 54 mg. daily, but an additional 25 mg. was required for long-term maintenance. Bradycardia, diarrhoea, and impotence were common side-effects; oedema also occurred, but less often. Bretylium was unsatisfactory because of tolerance, parotid pain, and effort syncope. Methyldopa was given by mouth in the long-term treatment of 15 patients. It was found that the main advantage of the drug was that the supine blood pressure was reduced as much as the standing pressure. Drowsiness and brady-

cardia were the chief side-effects. Paralytic ileus developed in one patient. The long-term results with methyldopa alone were disappointing. *C. T. Dollery*

111. Decarboxylase Inhibitors in the Treatment of Hypertension

A. N. BREST and J. H. MOYER. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 116-119, Jan., 1962. 2 figs., 12 refs.

Preliminary observations on the antihypertensive action of "methyldopa" are reported from the Hahnemann Medical College and Hospital, Philadelphia. In 10 out of 15 patients given parenteral doses there was a reduction in blood pressure beginning 2 to 4 hours after the dose. Drowsiness occurred in all 15 patients. Of 16 patients given long-term treatment with methyldopa by mouth, 3 had a significant fall in the supine blood pressure and 5 in the standing pressure. Drowsiness, orthostatic weakness, palpitations, and headache were frequent side-effects. *C. T. Dollery*

112. Clinical Evaluation of Hypertensive Patients. Indications for and Utilization of the Isotope Renogram, Separated Renal Function Study and Aorticorenal Arteriogram

J. C. HUNT, W. N. TAUXE, F. T. MAHER, L. F. GREENE, R. W. GIFFORD JR., and P. E. BERNATZ. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 134-140, Jan., 1962. 4 figs., 8 refs.

The authors briefly discuss the various procedures used in the diagnosis of unilateral renal disease secondary to hypertension and describe 4 cases seen at the Mayo Clinic. They state that the isotope renogram has served as an excellent screening procedure and that renal arteriography is highly desirable in making an anatomical diagnosis. [No details apart from the case reports are given.]

C. T. Dollery

113. Renovascular Hypertension. Experience with Renal Artery Reconstruction in 115 Patients

G. C. MORRIS JR., E. S. CRAWFORD, D. A. COOLEY, H. M. SELZMAN, and M. E. DEBAKEY. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 141-150, Jan., 1962. 7 figs., 10 refs.

Experience with renal artery reconstruction in 115 cases of renal vascular hypertension is described in this paper from Baylor University School of Medicine, Houston, Texas. The causative lesions in order of frequency were atherosclerosis of the main artery, occlusive disease of accessory arteries, fibromuscular proliferation (in young patients), and aneurysm of the renal artery. The excretion pyelogram, isotope renogram, and renal arteriography were found to be the most useful diagnostic procedures. The split-function test with ureteric catheters was less satisfactory because of a relatively high morbidity from infection and temporary renal suppression. The authors consider that a renal artery bypass with an 8 mm. "dacron" graft is the best operative procedure, but an autogenous saphenous vein has also been employed for bypass. Patch-graft angioplasty was used in 30% of the cases. In 80 of the 115 patients blood pressure was restored to within the limits normal for the patient's age.

[Few details are given in this brief account so that no judgement can be made on the methods and the results claimed.] *C. T. Dollery*

Clinical Haematology

ANAEMIA

114. **Prevalence of Anaemia in the General Population: a Rural and an Industrial Area Compared**
G. S. KILPATRICK. *British Medical Journal* [Brit. med. J.] 2, 1736-1738, Dec. 30, 1961. 9 refs.

This paper from the Welsh National School of Medicine, Cardiff, reports the results of a survey to determine the incidence of anaemia in an agricultural community in Wensleydale, Yorkshire. The sample studied included 412 men and women aged 15 years and over, and the findings were compared with those of a previous survey in an industrial community, the Rhondda Fach (*Brit. med. J.*, 1961, 1, 778; *Abstr. Wld Med.*, 1961, 30, 218). In comparable age groups the figures for haemoglobin, packed-cell volume, and mean corpuscular haemoglobin concentration in both sexes in Wensleydale were significantly lower than those for the Rhondda. The reason for this is not known.

The incidence of anaemia in males was 3.4% in the age group 15 to 24 years, zero in those aged 25 to 34, and rose steadily in older age groups to 25% in males aged 75 and over. In females the incidence of anaemia was 28% in the age group 15 to 24 years, falling to 12% in the age group 45 to 54, and rising to 21% in those aged 65 and over. The anaemia was mostly of the iron-deficiency type. As the author points out, the high incidence of anaemia in women aged 15 to 34 years (25 to 30%) is surprising and is probably related to menstruation and child-bearing. More unexpected is the high incidence of iron-deficiency anaemia in the older age groups in both sexes. Blood loss should always be suspected, but other factors, such as dietary insufficiency, may also be concerned. J. L. Markson

115. **Alkali-resistant Hemoglobin in Aplastic Anemia of Both Acquired and Congenital Types**
N. T. SHAHIDI, P. S. GERALD, and L. K. DIAMOND. *New England Journal of Medicine* [New Engl. J. Med.] 266, 117-120, Jan. 18, 1962. 4 figs., 10 refs.

It has been known for some time that the persistence of alkali-resistant or foetal haemoglobin is usually associated with certain genetically determined anaemias. There have also been reports of the presence of foetal haemoglobin in a number of acquired disorders. The evidence for this is somewhat conflicting, however, partly perhaps because examinations were carried out on patients who had had blood-transfusions, with consequent dilution of the foetal haemoglobin. In the study here reported from the Children's Hospital Medical Center (Harvard Medical School), Boston, 8 patients aged 2 to 15 years with acquired aplastic anaemia and 9 aged 6 to 15 with inherited aplastic anaemia have been examined. Of the 8 patients with acquired aplastic anaemia, which in 5 was probably due to treatment with chloramphenicol, increased levels of alkali-resistant haemoglobin were found ranging from 6 to 12%. In the 9 patients with constitutional aplastic anaemia the levels of foetal haemoglobin ranged from 3 to 15%. Repeated examinations later showed that in all these patients there

was still an increased level of foetal haemoglobin, although in some cases they had been in apparent remission for some time.

The alkali-resistant haemoglobin was examined also by electrophoretic analysis on agar gel and by ultraviolet spectroscopy and appeared to be identical with true foetal haemoglobin. It was noted that even the patients with acquired aplastic anaemia who had recovered spontaneously still had a raised level of alkali-resistant haemoglobin. Whether this level will eventually return to normal remains to be seen. The fluctuation and persistence of relatively high amounts of alkali-resistant haemoglobin in patients with congenital aplastic anaemia, even when in apparent haematological remission, suggests the presence of some permanent bone-marrow dysfunction. The family of one patient with congenital anaemia was investigated and 2 siblings were found with increased levels of alkali-resistant haemoglobin, both also showing a neutropenia as well as a mild thrombocytopenia. In one of these siblings a frank pancytopenia with anaemia developed 6 months later, suggesting that the persistence of alkali-resistant haemoglobin indicates an early biochemical abnormality. One of the patients with congenital aplastic anaemia died from secondary infection. Post-mortem examination of the liver and spleen showed no erythropoietic activity, a finding which suggested that the foetal haemoglobin was being produced in the bone marrow and not in the usual foetal sites of haematopoiesis. R. F. Jennison

116. **Effect of Food on the Absorption of Vitamin B₁₂**
S. SIEGEL, B. F. CHOW, K. OKUDA, S. CHEN, and E. J. HANUS. *American Journal of Clinical Nutrition* [Amer. J. Clin. Nutr.] 9, 705-707, Nov.-Dec., 1961. 3 refs.

The effect of pre-feeding on the absorption of vitamin B₁₂ (cyanocobalamin) was determined by comparing the 24-hour urinary excretion of radioactivity in 2 groups of healthy subjects given 50 µg. of radioactive vitamin B₁₂ by mouth, in one group 30 minutes after breakfast and in the other (control) after fasting since 4 p.m. the previous day. A statistically significant increase in excretion of 95% was found in the pre-fed group as compared with the controls, and the same result was found whether or not a "flushing-out" dose of 1,000 µg. of unlabelled vitamin B₁₂ was given intramuscularly. Studies in rats, in which the extent of absorption was judged by measuring radioactivity in liver and kidneys, gave similar results. F. W. Chattaway

117. **Twice Yearly Vitamin B₁₂ Therapy in Pernicious Anemia**
J. T. COLLINS and C. E. JACKSON. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 27-29, Jan., 1962. 5 refs.

This study, begun in 1953, was carried out on 8 patients with pernicious anaemia, of whom 6 were untreated and 2 were in remission. After initial intensive therapy with vitamin B₁₂ the untreated cases were treated by the same regimen as those in remission, namely, 1,000 µg. of the

vitamin given intravenously every 6 months. They were observed clinically and blood counts performed every 3 months [but serum vitamin-B₁₂ levels were not determined]. These patients were followed up for 2½ to 8 (mean 5½) years. All remained in clinical and haematological remission except for one patient who suffered temporarily from sore tongue, and none showed any evidence of neurological involvement. One patient died of a mesenteric thrombosis at the age of 83 and one was lost to follow-up after 4½ years. In 2 patients who did not come for treatment for 1½ and 2 years respectively there was no evidence of relapse, and in the patient who died post-mortem examination revealed no signs of degenerative disease of the spinal cord.

R. B. Thompson

118. Vitamin B₁₂ and Megaloblastic Anaemias in South African Bantu

J. METZ, V. BRANDT, and K. STEVENS. *British Medical Journal* [Brit. med. J.] 1, 24-27, Jan. 6, 1962. 4 figs., 12 refs.

In the South African Bantu megaloblastic anaemia occurs in women in association with pregnancy and also in malnourished infants in addition to Addisonian pernicious anaemia. At the South African Institute for Medical Research, Johannesburg, assay of serum vitamin B₁₂ in 81 Bantu patients with megaloblastic anaemia revealed that the levels of this vitamin were low in the 18 patients with pernicious anaemia, but usually within normal limits in the 44 patients with megaloblastic anaemia associated with pregnancy, in the 16 malnourished infants, and in 3 adults with nutritional megaloblastic anaemia. There was no correlation between the serum vitamin-B₁₂ levels and the degree of anaemia in the pregnant patients and the results of vitamin-B₁₂ therapy were unpredictable. The subsequent administration of folic acid, 30 mg. daily, produced full remissions in those not responding to treatment with vitamin B₁₂ as well as in those who received only folic acid. In the malnourished infants the administration of pharmacological doses of vitamin B₁₂ was usually found to induce remission.

It thus seems that the poor Bantu diet, often deficient in both animal protein and green leafy vegetable, does not commonly result in megaloblastic anaemia unless there is some superadded demand for antimegaloblastic factors. These increased demands tend to precipitate folic acid deficiency far more readily than vitamin-B₁₂ deficiency.

A. Ackroyd

119. Oral Treatment of Pernicious Anaemia with a Vitamin B₁₂/L-Glutamic Acid Mixture

J. G. HEATHCOTE and F. S. MOONEY. *Nature* [Nature (Lond.)] 193, 380-381, Jan. 27, 1962. 2 figs., 5 refs.

The authors of this preliminary communication from St. Helens Hospital, Lancashire, have demonstrated the beneficial action of a simple mixture of vitamin B₁₂ and L-glutamic acid given by mouth in the treatment of previously untreated pernicious anaemia in 2 cases, in which the diagnosis was proved by bone-marrow examination and the determination of the serum vitamin-B₁₂ levels. In both cases an initial reticulocytosis was obtained after oral treatment with 60 µg. of vitamin B₁₂ alone, but the haemoglobin values rose by only 3 and 1% respectively. After 10 days in one case and 13 days in the other 300 µg. of L-glutamic acid was given in addition to the vitamin B₁₂ and a secondary reticulocyte response occurred in both cases with a maximum

reticulocytosis of 10% and 13.4% on the 15th and 21st days respectively.

These results indicate that vitamin B₁₂ is more efficacious therapeutically when administered together with glutamic acid by mouth, and the authors suggest that they support their previous hypothesis that pernicious anaemia is due to a failure of gastric proteolysis and not to a lack of intrinsic factor, as originally postulated by Castle.

I. McLean Baird

120. Destruction of Erythrocytes; the Site of Haemolysis and Indications for Splenectomy in Haemolytic Anaemia. (Erythrozytendestruktion, Lokalisation der Hämolyse und Indikation zur Splenektomie bei hämolytischen anämien)

G. GEHRMANN and P. GROBEL. *Deutsche medizinische Wochenschrift* [Dtsch. med. Wschr.] 87, 76-81, Jan. 12, 1962. 13 figs., 17 refs.

The erythrocyte survival time was measured at the Medical Academy, Düsseldorf, using the patients' own cells labelled with radioactive chromium, in 22 patients with haemolytic anaemia of varying degrees of severity, of whom 13 had hereditary spherocytosis, one had hereditary non-spherocytic haemolytic anaemia, and 8 had acquired haemolytic anaemia. In all cases the half-life of the injected ⁵¹Cr-labelled cells was well below normal (28±4 days). Surface counting over the spleen and liver, carried out in order to determine the site of haemolysis, showed that the spleen was the main organ of haemolysis in all the patients with hereditary spherocytosis and in 5 of those with acquired haemolytic anaemia. Both spleen and liver were involved in 2 patients with acquired haemolytic anaemia; the site of the haemolysis could not be precisely located in the other cases. It is suggested that surface counting provides a useful method for selecting patients with haemolytic anaemia for splenectomy.

M. Lubran

121. Reticulocyte Destruction in Paroxysmal Nocturnal Haemoglobinuria

E. MYHRE and T. FLATMARK. *British Journal of Haematology* [Brit. J. Haemat.] 8, 48-56, Jan., 1962. 4 figs., 18 refs.

It has previously been demonstrated by Metz *et al.* (Brit. J. Haemat., 1960, 6, 372) that when a centrifuged blood specimen from a patient with paroxysmal nocturnal haemoglobinuria (P.N.H.) is incubated in acidified serum more haemolysis occurs in the reticulocyte-rich upper layer than in the reticulocyte-poor lower layer.

The present paper from the University Hospital (Rikshospitalet), Oslo, reports studies *in vitro* which confirm the observations of Metz and colleagues and make it plain that it is in fact the reticulocytes which are especially liable to destruction. Thus the authors found disproportionate lysis of reticulocytes during acid haemolysis of erythrocytes, whether or not the latter had been previously treated with thrombin. During incubation, which resulted in the lysis of 10 to 20% of the total erythrocyte population, 60 to 70% of the reticulocytes were destroyed. In a study *in vivo* they found that the intravenous injection of ⁵⁹Fe to a patient with P.N.H. resulted within 24 hours in an increased urinary excretion of labelled iron, which persisted for 2 more days and then declined. This finding is interpreted as evidence of premature destruction of newly labelled reticulocytes. It is suggested that in P.N.H. two erythrocyte populations are produced of which one is short-lived and does not survive the reticulocyte stage.

A. G. Baikie

HAEMORRHAGIC DISEASES

122. Hereditary Hypoprothrombinaemias

A. J. QUICK and C. V. HUSSEY. *Lancet* [*Lancet*] 1, 173-177, Jan. 27, 1962. 1 fig., 15 refs.

In this paper from Marquette University School of Medicine, Milwaukee, Wisconsin, the authors describe a study of 4 families, certain members of which had a genetically determined prolongation of the one-stage prothrombin time. [The original paper should be consulted for details of the technical methods employed.]

When a tissue extract and calcium are added to plasma, provided the fibrinogen concentration is normal, the resulting clotting time is known to be determined by the concentrations of prothrombin and Factors V, VII, and X. In one of the 4 families the diagnosis was straightforward, namely, a deficiency of Factor VII. In 2 further families the deficiency was in prothrombin, the precursor of thrombin. In these 2 families the prothrombin level, measured by a two-stage method, was very low and the prolonged one-stage clotting time was not shortened by adsorbed rabbit plasma or aged normal serum. The prolongation of the prothrombin time in the members of the remaining family was more difficult to explain in terms of current knowledge. In this family the prothrombin time was prolonged (controls 12 seconds, patients 16 seconds), but these patients had no haemostatic defect and they showed no deficiencies of prothrombin or of Factors V, VII, or X.

In their discussion the authors postulate that prothrombin occurs normally in a free and in an inactive form. The inactive prothrombin is converted to the free form by storing oxalated plasma in glass tubes at 4° C. for 24 to 48 hours. They suggest that in this asymptomatic prolongation of the one-stage prothrombin time the total prothrombin content is normal, but the free or active fraction is decreased. In patients with true prothrombin deficiency there is a lack of both the free and inactive forms. The authors conclude that the fixing of the ratio of active prothrombin to total prothrombin is genetically determined as a dominant and that this is mediated by a hitherto undescribed factor, the prothrombin-time-fixing agent (P.T.F.A.) or Hood factor, which was missing in the 4th family described.

A. S. Douglas

123. Autoimmune Thrombocytopenic Purpura ("ITP" Type) with Chronic Lymphocytic Leukemia

S. EBBE, B. WITTELS, and W. DAMESHEK. *Blood* [*Blood*] 19, 23-37, Jan., 1962. 2 figs., 43 refs.

The significance of the occurrence of thrombocytopenia during the course of chronic lymphocytic leukaemia is discussed. Usually the thrombocytopenia is due to crowding of the bone marrow by lymphocytes in the terminal stage of the leukaemia, megakaryocytes being few. Involvement of the spleen by the leukaemic process may produce hypersplenism with resultant thrombocytopenia. In this paper from Tufts University School of Medicine, Boston, 5 cases are reported in which thrombocytopenia was a feature of chronic lymphocytic leukaemia, in 4 of them purpura being the presenting manifestation. Megakaryocytes were plentiful in the marrow and the thrombocytopenia was shown to be of the idiopathic purpuric variety. In 3 of the cases there was gross splenomegaly, but hypersplenism, which is defined, was excluded. The presence of an extrinsic anti-

platelet factor is suggested. In 3 cases platelet survival time was shown to be very short (2 to 6 hours); platelet agglutinin demonstrated in the serum of one case, and megakaryocytes in another, took up fluorescein-labelled anti-human globulin. Of the 5 patients, 3 showed evidence of other autoantibodies, in the form of autoimmune haemolytic anaemia with a positive result in the Coombs test. A favourable response to steroid therapy was obtained in 3 cases; splenectomy was performed in one patient who had failed to respond to steroids; but no improvement in the platelet level resulted. Therapeutic measures themselves may be responsible for thrombocytopenia in chronic lymphocytic leukaemia, but in the present 5 cases, with one possible exception, there was no such relationship. In the exceptional case triethylene melamine may have been a factor; in this patient in the terminal phase thrombocytopenia was accompanied by autoimmune haemolysis. Reference is made to 7 similar cases described by Harrington and Arimura, in 5 of which platelet agglutinins were demonstrated.

The authors point out the analogous situation in which autoimmune haemolytic anaemia is a frequent complication of chronic lymphocytic leukaemia, thus suggesting that megakaryocytic thrombocytopenia in lymphoproliferative disorders may be one aspect of a broad spectrum of immunologic abnormalities. The demonstration of this type of thrombocytopenia allows of a better prognosis and is of therapeutic significance. Experience suggests that steroid therapy is effective in about half of such cases, while splenectomy produces remission in one-quarter. The use of x-ray therapy or alkylating agents is inadvisable. In the megakaryocytic type of thrombocytopenia platelet transfusion and control of the leukaemic process are necessary, though large doses of corticosteroids may cause regression of the proliferative process with increase of platelet level.

A. Brown

LEUKAEMIA

124. The Seasonal Incidence of Acute Leukemia: a Contribution to the Epidemiology of the Disease

D. M. HAYES. *Cancer* [*Cancer* (Philad.)] 14, 1301-1305, Nov.-Dec., 1961. 5 figs., 17 refs.

Seasonal variation in the onset of acute leukaemia may be interpreted as evidence of an infectious aetiology, although, as is pointed out in this paper, this is not the basis of seasonal variation in the incidence of deficiency diseases and others of dietary cause. The author reviews several reports of winter peaks in the onset of acute leukaemia as well as the evidence for seasonal variations in the ease of transmission of fowl leucosis. At the North Carolina Baptist Hospital, Winston-Salem, 184 patients with acute leukaemia were seen between 1943 and 1958. It was thought to be impossible to determine the month of onset of symptoms from hospital records, and so the month of histological diagnosis was used instead.

There appeared to be a peak incidence in the winter and early spring months ($P < 0.1$). When the 184 cases were further analysed by age, sex, and cytological type of leukaemia, none of these categories was seen to make any special contribution to the apparent seasonal variation. The seasonal incidence of acute leukaemia was compared with that of measles, whooping-cough, and scarlet fever in

North Carolina, and also that of undifferentiated respiratory infections; no temporal association could be discerned between the incidence of acute leukaemia and that of the other diseases.

The author refers to seasonal variations in the organ weights of laboratory animals, and it is pointed out that seasonal variations in the diagnosis of human acute leukaemia in North Carolina bear an inverse relationship to seasonal changes in the weights of the endocrine organs of some laboratory animals.

A. G. Baikie

125. Chromosome Studies in Human Leukemia. I. Acute Leukemia in Children

D. A. HUNGERFORD. *Journal of the National Cancer Institute [J. nat. Cancer Inst.]* 27, 983-1011, Nov., 1961 [received Jan., 1962]. 10 figs., 17 refs.

In these chromosome studies, carried out at the Institute for Cancer Research, Philadelphia, on 7 children with acute leukaemia whose ages ranged from 3 months to 11 years short-term cultures of peripheral blood leucocytes were used in 6 cases and both bone marrow and peripheral leucocytes in the 7th; in 3 cases no treatment had yet been given at the time of the investigation. One of the children had one sib who was a mongol and another sib who had congenital heart disease. In all 7 cases the chromosomes were counted in at least 52 cells and detailed analyses were carried out on between 5 and 15 cells.

No abnormality of chromosome count distribution was found, but in 6 cases there was a minority of cells of abnormal karyotype. There was no evidence of the occurrence of a specific chromosome abnormality in children with acute leukaemia and no obvious tendency for particular chromosomes to be involved in the abnormalities found. The author relates the number of cells of abnormal karyotype to the duration of the disease and to whether or not the patient had been treated at the time of study; thus the frequency was 3 out of 33 cells in untreated cases and 8 out of 30 cells in treated cases. He concludes that the changes observed in this study were secondary changes and that whatever primary changes may be associated with the occurrence of acute leukaemia in children are not demonstrable by current methods.

A. G. Baikie

126. Chromosome Studies in Human Leukemia. II. Chronic Granulocytic Leukemia

P. C. NOWELL and D. A. HUNGERFORD. *Journal of the National Cancer Institute [J. nat. Cancer Inst.]* 27, 1013-1035, Nov., 1961 [received Jan., 1962]. 14 figs., 10 refs.

This further paper from the University of Pennsylvania [see Abstract 125] reports the results of chromosome studies in 10 cases of chronic myeloid leukaemia. Here the patients' ages ranged from 9 to 80 years, and the stage of their disease from the untreated and asymptomatic to the stage of acute leukaemic change. As before, the studies were carried out on short-term cultures of peripheral-blood leucocytes in 9 cases and preparations of bone marrow in 2 cases.

In all the cases studied the modal chromosome number was 46 and the Ph¹ (Philadelphia) chromosome was seen in 9 of the 10 cases. The one case in which the Ph¹ chromosome was not present was studied during a therapeutically induced remission in the phase of acute leukaemic change; in this case another small acrocentric chromosome, probably

one of Pair 22, was seen to be smaller than its homologue. In one of the 9 cases in which the Ph¹ chromosome was present some cells carried a second abnormal small acrocentric chromosome, but this additional abnormality the authors attribute to the previous radiotherapy given to this patient. It was noted that after culture of the peripheral blood from these cases of chronic myeloid leukaemia few normal divisions were seen after 48 hours, whereas at the end of 72 hours dividing cells of a normal chromosome constitution were much more numerous. It was also found that the cells in chronic myeloid leukaemia grow better in homologous than in autologous plasma. The authors consider it likely that the Ph¹ chromosome arises as a consequence of deletion from the long arms of one chromosome of Pair 21 rather than as a result of reciprocal translocation. They regard the chromosome abnormality as the primary change in the cells of chronic myeloid leukaemia and not as a secondary change.

A. G. Baikie

127. Immunologic Factors and Resistance to Infection in Chronic Lymphatic Leukemia

D. G. MILLER and D. A. KARNOFSKY. *American Journal of Medicine [Amer. J. Med.]* 31, 748-757, Nov., 1961. 1 fig., 38 refs.

Patients with chronic lymphatic leukaemia are especially susceptible to infections and nearly as many die of infectious disease as die of haematological complications. In an attempt to elucidate this liability to infection a study was carried out at the Sloan-Kettering Institute for Cancer Research, New York, on 22 such patients who were assigned to one of two groups according to whether they had shown a special liability to infections (Group A) or not (Group B), similar observations being made on 20 patients with other neoplastic diseases (Group C).

No significant difference was found between the two groups of patients with chronic lymphatic leukaemia in regard to total leucocyte count, absolute number of mature granulocytes, hepato-splenomegaly or lymphadenopathy, their response to a variety of antigens, or in serum levels of iso-haemagglutinins, complement, and properdin. On the other hand the patients in Group A had notably low γ -globulin levels, whereas those in Groups B and C had normal or elevated levels. Lower values for γ -globulin appeared to be associated with increased levels of macroglobulins. Hypogammaglobulinaemia in chronic lymphatic leukaemia is not clearly related to the duration of the disease, but may be otherwise associated with a later stage in the natural history of the disorder. There was no apparent relationship between hypogammaglobulinaemia and previous treatment. The authors point out that in these patients with chronic lymphatic leukaemia serum γ -globulin levels of 0.7 g. per 100 ml. or less were associated with chronic or recurrent infection, in contrast with the finding in patients with congenital hypogammaglobulinaemia, in whom very much lower γ -globulin levels may occur without concomitant infection. The relationship between hypogammaglobulinaemia and infection in chronic lymphatic leukaemia is obviously obscure, especially since antibody production is apparently unaffected. The differing abnormal serum protein patterns in chronic lymphatic leukaemia are discussed in relation to the morphological cytology of the disease and it is postulated that more than one type of the disease may exist.

A. G. Baikie

Respiratory System

128. Spontaneous Pneumothorax: a Study of Ninety-four Cases

I. LENOX-SMITH. *British Journal of Diseases of the Chest* [Brit. J. Dis. Chest] 56, 1-10, Jan., 1962. 3 figs., 1 ref.

This is an analysis of 94 consecutive cases of spontaneous pneumothorax treated at the Southampton Chest Hospital between 1955 and 1960, both primary and secondary cases being included. The author comments on age and sex incidence, relationship to smoking and to type of work, mode of onset, and diagnostic difficulties. Dyspnoea was the commonest symptom, occurring in 76 cases; chest pain was present in 56 cases. Proved recurrences were observed in 24 cases.

The methods of treatment varied and the results are compared. Expectant treatment was accompanied by a 51% recurrence rate and is therefore not recommended. The recurrence rate fell to 18% with simple aspiration, and was nil in 5 cases with effusions which were treated by aspiration of both air and fluid. Treatment with a rubber intercostal catheter connected to an underwater drain had no advantage over aspiration, but increased the risk of effusion and secondary infection. The instillation of camphor in oil, poultage, and thoracotomy, though painful procedures, satisfactorily reduced the recurrence rate. K. C. Robinson

129. Idiopathic Fibrous Mediastinitis

L. HACHE, L. B. WOOLNER, and P. E. BERNATZ. *Diseases of the Chest* [Dis. Chest] 41, 9-25, Jan., 1962. 10 figs., 25 refs.

Fibrous mediastinitis has been recognized as a disease entity for more than half a century. At the turn of the century and in subsequent decades it paralleled then prevalent and notoriously sclerogenic tuberculous and syphilitic infections. In recent decades, similar exuberant fibrous processes are observed, but some are of rather nebulous origin and are therefore considered idiopathic.

Obstruction of the superior vena cava is the hallmark of this disease. It has been estimated that 10 to 23% of such obstructions are due to fibrous mediastinitis. Of 20 Mayo Clinic patients with the so-called idiopathic variety diagnosed on the basis of surgical exploration or necropsy, 12 had either complete or partial superior vena caval obstruction, 4 had involvement of the tracheobronchial tree, 2 had esophageal obstruction, one died of stenosis of the pulmonary vein, and one had fibrosis as an incidental finding at necropsy.

Grossly the process usually assumes the form of a diffuse and adherent woody mass of fibrosis, but occasionally a circumscribed localized type is also encountered, which can be removed surgically with relative ease. Histologically, nothing more is seen than an inflammatory mass of fibrous tissue in various stages of maturity, ranging from young fibroblastic tissue intermixed with inflammatory cells to ancient and hyalinized collagen. The process is most probably an exaggerated reparative fibroblastic reaction secondary to mediastinal adenopathy or to direct spread of inflammation from infections of the upper and lower parts

of the respiratory tract. Less commonly it may result from haemorrhage, from rheumatic fever or unknown acute mediastinitis. All of this appears to take place in a patient with great proclivity to form excessive fibrous tissue such as may be observed in other phases of surgery in the form of exuberant scars and adhesions.

Surgical treatment is concerned mainly with superior vena caval obstruction, the effective relief of which still awaits further perfecting of grafting material and procedures. The over-all prognosis is good, as the disease progresses very slowly and the complication results usually from the slow contraction of scar tissue. Exception is made in stenosis of the pulmonary vein: all 6 patients so affected died of this complication.—[Authors' summary.]

LUNGS AND BRONCHI

130. Clinical Trial of Methyl Cysteine Hydrochloride in Chronic Bronchitis

K. N. V. PALMER, M. R. GEAKE, and W. BRASS. *British Medical Journal* [Brit. med. J.] 1, 280-282, Feb. 3, 1962. 19 refs.

Cysteine has been shown to assist healing of skin wounds when applied topically. Methyl cysteine hydrochloride is a stable derivative of cysteine which can be given as an aerosol or taken orally as a tablet. When given by mouth to animals the content of sulphur in the lungs increases, and in rabbits the bronchial secretion provoked by an irritant aerosol is reduced. Good results in human disease have been reported from France and the drug is non-toxic.

With the assistance of general practitioners in the Aberdeen and Preston regions a double-blind trial of methyl cysteine hydrochloride ("acdrile") was made in 164 men with chronic bronchitis, 82 receiving the drug and 82 acting as controls. The dose was 2 tablets swallowed 3 times daily before meals for a month. [The amount of methyl cysteine hydrochloride in each tablet is not given.] There was a significant reduction in cough and sputum in patients taking the drug as compared with the controls, but no difference was observed in dyspnoea, wheeze, rales, or rhonchi.

Arthur Willcox

131. Effect of Oral Alpha-chymotrypsin on Sputum Viscosity

R. A. BRUCE and K. C. QUINTON. *British Medical Journal* [Brit. med. J.] 1, 282-284, Feb. 3, 1962. 2 figs., 11 refs.

Alpha-chymotrypsin ("chymoral") is a preparation of trypsin, a proteolytic enzyme, which can be taken orally. In a double-blind trial of its action conducted at the Cambridge Chest Clinic 21 patients with chronic bronchitis took 2 tablets of the drug [strength not stated] 4 times daily for 4 weeks, while 19 patients acted as controls. The viscosity of the sputum was measured weekly. While the sputum viscosity did not change significantly in the controls, in those taking the drug it was considerably reduced, the figures at the end of the 4th week of treatment compared with the

initial reading being -6.3% for the former as against -68.3% for the latter. Patients in both groups, however, claimed symptomatic improvement. *Arthur Willcox*

132. Pulmonary Eosinophilic Granuloma: Its Natural History and Prognosis

J. N. BICKERS, H. A. BUECHNER, and P. J. EKMAN. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 211-219, Feb., 1962. 7 figs., 8 refs.

Five patients with pulmonary eosinophilic granuloma are described. In 4, the disease appeared to be limited to the lungs; and, in one, there was also involvement of the right pubic ramus. Follow-up observations on 3 additional and previously reported cases are presented. The clinical course of the disease in these patients tends to confirm the concept that the active phase of pulmonary eosinophilic granuloma is usually self limited and that the disorder carries a predominantly favorable prognosis. However, in some cases extensive pulmonary fibrosis and emphysema may occur, with resulting impairment in pulmonary function of an intense degree. There is reason to believe that eosinophilic granuloma of the lungs is much more common than is generally supposed and that this condition is worthy of consideration in all patients with diffuse, indeterminate pulmonary lesions.

The natural history of the disease is discussed briefly and some thoughts are expressed regarding its etiology. According to present evidence, some type of hypersensitivity state appears to offer the best explanation for the tissue changes which characterize this disorder.—[Authors' summary.]

133. Current Problems of the Pneumonias

H. A. REIMANN. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 144-154, Jan., 1962. 2 figs., bibliography.

134. Conservatism in Surgical Treatment of Bronchial Carcinoma: a Review of 826 Personal Operations

G. FLAVELL. *British Medical Journal* [Brit. med. J.] 1, 284-287, Feb. 3, 1962. 15 refs.

In this [somewhat discursive] report from the London Hospital the author describes his experience of the operative treatment of 826 cases of bronchial carcinoma. A resectability rate of 70% (570 cases) was obtained, and all cases in which there was no absolute contraindication to operation (such as extrathoracic dissemination, hoarseness, dysphagia, superior vena caval obstruction, Horner's syndrome, phrenic paralysis, or recurrent effusion) were explored. The proportion of men to women was 11 to 1, and of the men 21% were aged 41 to 50 years, 40% 51 to 60 years, and 28% 61 to 70 years—thus 90% were in the age group 41 to 70 years. The left upper lobe was involved in 31% of cases, the right upper or lower lobes in 23% each, the left lower lobe in 18%, and the middle lobe in 5%. In 65% of the resected cases the growth had already spread to the visceral pleura, regional lymph nodes, blood vessels, or chest wall. In one-quarter of the patients who survived for 5 years or more the growth was not originally confined to the lung, and in 8% the chest wall or mediastinum had been invaded. Early symptoms were an alteration in the character of the cough, pain or discomfort in the chest, a febrile chest illness, blood-stained sputum, or sudden dyspnoea. Pain was the second commonest early symptom. Hypertrophic pulmonary osteoarthropathy was a feature,

often the presenting one, in 13% of cases. The high incidence of malignant lung abscess is emphasized. In the author's view patients should not be rejected for operation on radiological grounds alone, unless vertebral or rib-neck erosion is present.

In this series pneumonectomy was performed in 299 cases, lobectomy in 266, and segmental resection in 5; it is noted that the proportion of lobectomies was considerably higher than that in other reported series. The hospital operative mortality was 5.6% and the bronchopleural fistula rate 1.4%. The type of tumour was adenocarcinoma in 10% of cases, the remainder being squamous or anaplastic carcinoma. Of the 273 patients treated by resection 5 or more years ago, 107 survived less than one year, 44 for one year, 10 for 2 years, 13 for 3 years, 10 for 4 years, and 89 for 5 or more years. Thus 41% survived more than 3 years and 32.6% more than 5 years. The majority of recurrences took place within one year. *R. L. Hurt*

135. The Apparent Sites of Origin of Carcinomas of the Lung

L. H. GARLAND, R. L. BEIER, W. COULSON, J. H. HEALD, and R. L. STEIN. *Radiology* [Radiology] 78, 1-11, Jan., 1962. 10 figs., 6 refs.

The records of patients with bronchogenic carcinoma at 4 hospitals in San Francisco over 5 to 10 years were reviewed in an attempt to identify the site of origin of the carcinoma. Only 150 out of 463 cases were found suitable for reasonable identification.

The apparent site was the main bronchus in 16 cases, a lobar bronchus in 44, a segmental bronchus in 44, and a segmental region, the exact bronchial origin not being established, in 46 cases. The ratio of adenocarcinoma to other types of neoplasm was highest (16:30) in the last-mentioned region. On the basis of bronchographic measurements of parts of the left bronchial tree it is estimated that the surface area of the main bronchus is 16.5 sq. cm., of the two lobar bronchi 12 sq. cm., and of the lower-lobe segmental and subsegmental bronchi 150 sq. cm. This suggests that the higher incidence of carcinoma in the last two areas may be explained by the larger surface area at risk. *B. Golberg*

136. Endocrine and Certain Other Changes in Men with Carcinoma of the Lung

M. J. WILLIAMS and S. C. SOMMERS. *Cancer* [Cancer (Philad.)] 15, 109-117, Jan.-Feb., 1962. 8 figs., 29 refs.

A comparative study was made of autopsy material from 100 men with lung carcinoma, from 50 men with cancer of other sites, and from 50 men without cancer. All were of comparable age and origin. Changes observed histologically in lungs, endocrine glands, and target organs were compared and analysed statistically. Underlying chronic lung disease was more common with lung cancer than in either control group. Salient endocrine peculiarities observed were indications of pituitary-adrenocortical hyperfunction with both bronchogenic and other cancers, evidence of persisting normal testicular activity with squamous cell carcinoma of lung, an increase in circulating corticoids with oat cell carcinoma, and various abnormalities, probably reflecting estrogen effects, in men with bronchogenic adenocarcinomas. Host factors appeared important in relation to the type of bronchogenic carcinoma that developed.—[Authors' summary.]

Urogenital System

137. Adjustment of Urine pH in the Chemotherapy of Urinary-tract Infections: a Laboratory and Clinical Assessment

W. BRUMFITT and A. PERCIVAL. *Lancet* [*Lancet*] 1, 186-190, Jan. 27, 1962. 2 figs., 22 refs.

The authors, at Edgware General and St. Mary's Hospitals, London, have studied the effect of adjusting the urinary pH in treating urinary infections with various antibiotics. Studies *in vitro* showed that streptomycin, neomycin, kanamycin, penicillin, and erythromycin had most effect at alkaline pH on various organisms. At acid pH the tetracyclines, cycloserine, and novobiocin were more effective. In the case of sulphonamides and chloramphenicol the results varied with different organisms. The activity of nitrofurantoin on the other hand was not changed with pH adjustment.

A clinical randomized trial was then conducted, 102 patients being treated with various antibiotics but without pH adjustment, and 102 with pH adjustment in addition, according to studies *in vitro* of the particular offending organism. In 67% of the first group and in 87% of the second the urine became sterile; excluding patients treated with nitrofurantoin these figures become 64% and 91% respectively. Of 136 other patients who had relapsed after a course of chemotherapy, re-treatment with pH adjustment gave favourable results in 81%.

The authors' findings appear to indicate the importance of pH adjustment in the treatment of infections of the urinary tract.

Arnold Pines

138. A Clinicopathological Study of the Nephrotic Syndrome

R. R. BURCH, M. A. PEARL, and W. H. STERNBERG. *Annals of Internal Medicine* [*Ann. Intern. Med.*] 56, 54-67, Jan., 1962. 11 figs., 41 refs.

This paper from Tulane University School of Medicine and the Charity Hospital of Louisiana, New Orleans, describes the results of percutaneous renal biopsy studies on 33 patients with the nephrotic syndrome due to primary renal disease and correlates the histological findings with the clinical response to steroid therapy in 19 of these. On histological grounds the cases were classified in 5 groups: (1) membranous glomerulonephritis (10 cases); (2) proliferative glomerulonephritis (5 cases); (3) membranous and proliferative glomerulonephritis (6 cases); (4) chronic sclerosing glomerulonephritis (6 cases); and (5) an "indeterminate" group (6 cases), in which the glomeruli appeared to be normal on light microscopy or showed minimal membranous or proliferative changes. [This last group apparently corresponds to the so-called "minimal change group" of Blainey *et al.* (*Quart. J. Med.*, 1960, 29, 235; *Abstr. Wld Med.*, 1961, 29, 32).] There was some overlap of the ages of the patients in the various groups, although the mean age was lowest (17 years) in Group 5, which included most of the children in the series.

The patients were observed for periods from 6 months to 5 years and were treated with restricted physical activity and

a low-sodium diet. To all except those with far-advanced or terminal disease and those who could not be supervised adequately prednisone, 40 mg. daily, was given for 4 weeks. If no response occurred (as judged by a reduction in daily proteinuria and the return of serum albumin and cholesterol levels towards normal) the prednisone was gradually discontinued; otherwise the prednisone was continued until there was no further improvement, when it was either gradually discontinued or a maintenance dose given sufficient to suppress any relapse. Response to treatment with prednisone varied from group to group. Of the 6 patients in Group 1 so treated, there was diminished proteinuria in 4, a complete remission in 1, and no response in 1. Of 4 patients in Group 2 there was complete remission in 3 and no response in 1. Of 3 patients in Group 3, only 1 showed a reduction in proteinuria and there were no remissions. Of 2 patients in Group 4, 1 showed a reduction in proteinuria, but again there were no remissions. Of 4 patients in Group 5 treated with prednisone, all responded and in 3 there was a complete remission. Remissions thus occurred most frequently in Groups 2 (75%) and 5 (75%), were infrequent in Group 1 (16%), and did not occur at all in Groups 3 and 4.

The authors suggest that since serious complications may arise from the use of steroids in the treatment of the nephrotic syndrome it would be advisable to treat only those patients considered, in the light of the initial renal histological findings, likely to respond favourably.

Hewett A. Ellis

139. Atrophic Pyelonephritis from Ureteral Reflux without Obstructive Signs ("Reflux Pyelonephritis")

F. HINMAN JR. and J. A. HUTCH. *Journal of Urology* [*J. Urol. (Baltimore)*] 87, 230-242, March, 1962. 13 figs.

140. The Blood-Cerebrospinal Fluid Barrier in Uremia

R. B. FREEMAN, M. F. SHEFF, J. F. MAHER, and G. E. SCHREINER. *Annals of Internal Medicine* [*Ann. intern. Med.*] 56, 233-240, Feb., 1962. 3 figs., 18 refs.

This paper from the Pennsylvania Hospital, Philadelphia, and the Georgetown University Hospital and School of Medicine, Washington, D.C., reports a comparison in 14 patients with chronic and 5 with acute uraemia between the concentrations in plasma and cerebrospinal fluid (C.S.F.) of protein, uric acid, urea, creatinine, phosphorus, and (after loading) bromide. There was some tendency for the concentrations in the C.S.F. to rise to levels nearer to those in the plasma; this was notable for bromide and also for phosphorus. Some relation was also found between a high concentration of phosphorus in the C.S.F. and the occurrence of muscular twitching. The findings bore no apparent relation to the mental changes.

[The C.S.F. protein content was appreciably elevated in some patients, including those with high ratios for bromine; since the patients' blood pressure is not recorded the part played by hypertensive damage in producing these results is not clear.]

D. A. K. Black

Endocrinology

141. **Secretion in the Neurones of the Hypothalamic Nuclei on Administration of Cortisone and ACTH.** (Секреция в нейронах ядер гипоталамуса при введении кортизона и АКГГ)

Е. И. ЗУБКОВА. *Проблемы Эндокринологии и Гормонотерапии* [Probl. Endokr. Gormonoter.] 8, 21-27, Jan.-Feb., 1962. 4 figs., 24 refs.

The part played by the hypothalamic nuclei in regulating the function of the anterior lobe of the pituitary gland is a problem to which much attention has recently been given. It has been established that a neurosecretion can pass from the supraoptic and paraventricular nuclei to the infundibulum and thence to the anterior lobe, this transport being carried out partly by the blood vessels and partly by "wandering cells" which migrate from the hypothalamus to the hypophysis. To clarify this problem further the author has studied the secretory process in puppies at two early stages of postnatal development (ages 1½ and 4 months) and the effect of cortisone and corticotrophin (ACTH) upon it, a total of 24 puppies from 4 litters being employed in the investigation.

In the hypothalamus of puppies aged 1½ months the neurones were found to be still imperfectly differentiated and there were few granules of the neurosecretion (which stains with Gömöri's aldehyde fuchsin stain), these being notably rare in the supraoptic nuclei. At the age of 4 months, however, the cells have acquired their characteristic form and were full of secretory granules; Hering's bodies and "wandering cells", also full of granules, were seen lying at the base of the ependymal cells of the third ventricle and in the walls of the infundibulum. The administration of cortisone accelerated the differentiation of the supraoptic and paraventricular neurones in all puppies, and increased the number of granules in the bodies and axons of the neurones and also the number of wandering cells, the latter being seen to penetrate well into the adenohypophysis. The neurones themselves were smaller than those in the untreated animals, and the ribonucleic protein granules were grouped around the nucleus instead of being mostly at the periphery of the cell. The effect of ACTH on the younger puppies was shown by an enlargement of the nerve cells, with a very scanty amount of granules. In the older puppies the secretory activity was retarded and the amount of secretion in the neurones and in the hypophysis was diminished.

L. Firman-Edwards

142. **Calcitonin—a Hormone from the Parathyroid which Lowers the Calcium-level of the Blood**

D. H. COPP and B. CHENEY. *Nature* [Nature (Lond.)] 193, 381-382, Jan. 27, 1962. 1 fig., 5 refs.

From the University of British Columbia, Vancouver, the authors describe experiments in dogs which have led to the discovery of a new humoral agent which lowers the level of calcium in the blood. This substance, which has been named "calcitonin", appears to be fast-acting and short-lived. Perfusion experiments have shown that when blood containing a high concentration of calcium was perfused

through the parathyroid glands it caused a dramatic fall in the calcium level in the systemic blood within 15 minutes, while perfusion with blood of low calcium concentration produced a typical rise in the systemic blood calcium level. When the parathyroid glands were removed the authors found to their surprise that instead of the blood calcium level falling it continued to rise, and in one case remained elevated for more than 15 hours.

These results, confirmed in 8 dogs, indicated that hypercalcaemia does not merely suppress the production of parathyroid hormone, but also stimulates the parathyroid glands to produce a humoral agent which lowers the calcium level of the blood. This dual hormone mechanism, which the authors compare with the analogous control of blood sugar levels by insulin and glucagon, accounts for the precise manner in which the blood calcium level is controlled.

I. McLean Baird

THYROID GLAND

143. **Loss of Tissue-specific Autoantigens in Thyroid Tumours**

R. B. GOUDIE and H. M. MCCALLUM. *Lancet* [Lancet] 1, 348-352, Feb. 17, 1962. 3 figs., 11 refs.

In the immunological theory of tumour formation it is postulated that cells escape from the restraining influence of autoantibodies. The present study from the Western Infirmary, Glasgow, indicates that there is a lack of tissue-specific antigens in the cells of certain thyroid tumours. It has been shown by Pulvertaft *et al.* (*Lancet*, 1959, 2, 214; *Abstr. Wld Med.*, 1960, 27, 128) that a cytotoxic antithyroid autoantibody is formed naturally in cases of Hashimoto's disease in man.

The authors found that the electrophoretic mobility of this autoantibody was consistent with its being a γ globulin, and that it was absorbed by an extract of a thyrotoxic thyroid gland, but not by an extract of an adenomatous nodular goitre. The antibody prevented the spread of both normal and hyperplastic thyroid epithelial cells in tissue culture, possibly by reacting with microsomal tissue-specific autoantigen in the presence of complement (fresh guinea-pig serum). The antibody, however, did not prevent the spread of some of the cells of simple and malignant thyroid tumours in tissue culture, possibly because they are deficient in the tissue-specific autoantigen concerned.

G. B. West

144. **Thyrotoxic Myopathy: a Reappraisal and Report of Three Cases**

C. W. H. HAVARD. *British Medical Journal* [Brit. med. J.] 1, 440-443, Feb. 17, 1962. 5 figs., 18 refs.

As there is no reliable pattern of biochemical or histological change in thyrotoxic myopathy, and electromyographic signs of myopathy may occur in thyrotoxic patients without obvious muscle-wasting and with only slight weakness, the diagnosis of this disorder may be difficult. In this paper from St. Bartholomew's Hospital, London, it is sug-

gested that the diagnosis must depend on the demonstration of localized muscle weakness and wasting which returns to normal after the correction of the hyperthyroid state. Three cases are described, in one of which the muscular weakness was the presenting complaint and the thyrotoxicosis was masked; in the second case muscular weakness was one of many thyrotoxic symptoms; while in the third the other symptoms of thyrotoxicosis were so overwhelming that the muscular weakness passed unnoticed. Urinary creatine excretion was highest in the patient with least muscular wasting, while the electromyogram was normal in one patient with obvious myopathy. In all 3 patients control of the hyperthyroid state was associated with the return to normal of the localized muscular weakness and wasting.

The author suggests that the atrophy of muscles so commonly seen in hyperthyroidism together with complaints of weakness is really the result of myopathy rather than part of the general asthenia.

B. M. Ansell.

145. Suppression of Release of Radioactive Iodine as a Test of Thyroid Function

R. ECKLUND and R. RYAN. *Journal of Clinical Endocrinology and Metabolism* [J. clin. Endocr.] 22, 26-30, Jan., 1962. 1 fig., 11 refs.

In normal subjects the administration of thyroid hormone reduces the rate of discharge of administered radioactive iodine from the thyroid gland, whereas no such effect is seen in hyperthyroid patients. This difference in response has now been used by the authors at the University of Illinois College of Medicine, Chicago, as a diagnostic test for hyperthyroidism. It was performed as follows: 24 hours after an oral dose of ^{131}I (15 to 50 μc .) the thyroidal radioactivity was measured. Triiodothyronine, 25 μg . every 8 hours, and methimazole, 30 mg. every 6 hours, were then administered and thyroidal radioactivity again determined at 48, 72, or 96 hours and once more at 144, 168, or 192 hours, the values recorded being expressed as a percentage of the 24-hour uptake.

In 16 euthyroid subjects (5 with small goitres) and 19 patients in whom the diagnosis of hyperthyroidism had already been established who were so tested a significant difference in the thyroid radioactive iodine level after the administration of thyroid hormone was apparent between the two groups from 72 hours after the tracer dose of radioiodine had been given. The separation between the groups was greater, the longer the interval between radioisotope administration and the final uptake study. As a 7-day interval is administratively convenient this was chosen for final analysis. The mean percentage of radioiodine remaining in the gland at 7 days after its administration was 92.1 in the euthyroid group and 49.1 in the hyperthyroid group. There was no overlap between the individual results in the two groups, but 2 patients with recurrent hyperthyroidism following thyroidectomy showed some slowing of the rate of discharge of radioiodine from the gland. By this means 2 euthyroid subjects with a rapid rate of release of ^{131}I were discovered; of these subjects, one, with rheumatoid arthritis, had a goitre and exophthalmos, while the other had Hashimoto's disease. Advantages of this test over that based on the failure of thyroid hormone to suppress uptake of ^{131}I by the hyperthyroid gland include the absence of delay in starting antithyroid therapy and the need for only one dose of the radioactive isotope.

H.-J. B. Galbraith

146. Thyroid Nodules Occurring Late after Treatment of Thyrotoxicosis with Radiiodine

G. E. SHELLE, S. LINDSAY, K. R. MCCORMACK, and M. GALANTE. *Journal of Clinical Endocrinology and Metabolism* [J. clin. Endocr.] 22, 8-18, Jan., 1962. 12 figs., 26 refs.

Among 256 patients with toxic diffuse goiter treated with radioiodine between 1946 and 1953, there were 8 patients in whom thyroid nodules developed between 5 and 14 years after the ^{131}I therapy. Thyroidectomy in each of the 8 patients showed multiple nodules as well as effects attributable to irradiation. The frequency of occurrence of the late nodules was much higher in the younger patients, the highest frequency being in those less than 20 years of age at the time of treatment. These nodules appeared to originate in hyperplastic regenerating areas of thyroid epithelium and were thought to be due to a stimulatory effect of thyrotropin acting on thyroid tissue still capable of proliferating despite injury by irradiation. Development of the thyroid nodules or adenomas in the 8 patients closely paralleled the development of nodules as described in irradiated rat thyroids. Except for a single invasive adenoma in 1 patient, there was no evidence of malignancy in these human thyroid glands.—[Authors' abstract.]

147. Neurologic Manifestations of Myxedema

V. SANDERS. *New England Journal of Medicine* [New Engl. J. Med.] 266, 547-552, March 15, and 599-603, March 22, 1962. Bibliography.

ADRENAL GLANDS

148. The Water Loading Test for the Diagnosis of Adrenocortical Insufficiency

A. JADRESIC, M. CARRASCO, and E. LÓPEZ. *Lancet* [Lancet] 1, 401-402, Feb. 24, 1962. 9 refs.

The authors have further modified Kepler's water-loading test for adrenal insufficiency by introducing several practical improvements, and consider the test to be a useful laboratory aid. The subject under test, having taken no food or drink overnight, empties his bladder and then drinks one litre of water within 15 minutes. Urine is voided every 30 minutes for 2 hours and the total volume measured. From the University of Chile, Santiago, they here report the results of the test as carried out on 28 normal subjects, 21 patients with Addison's disease, and 7 patients with pituitary deficiency, all treatment having been stopped for 48 hours before the test. In addition 26 patients with myxoedema were tested after treatment had been withheld for one week.

The normal subjects excreted 70% of the fluid intake, whereas patients with adrenal or pituitary deficiency excreted less than 55%. Myxoedematous patients showed a low output, but not as low as the adrenal cases. The authors state that a normal response to this water-loading test excludes adrenal insufficiency, whereas a subnormal response may be due to various causes. The administration of 50 mg. of cortisone 4 hours before the test usually produced, in patients with Addison's disease or hypopituitarism, a correction of the low urine flow, but occasionally patients required more prolonged treatment. Cortisone caused but slight improvement in cases of myxoedema, whereas treatment with thyroid extract brought about full correction in urine flow.

Nancy Gough

149 (a). The Blocking by Spirolactones of the Actions of Aldosterone and Cortisol upon the Human Kidney
J. N. MILLS, S. THOMAS, and K. S. WILLIAMSON. *Journal of Endocrinology [J. Endocr.]* 23, 357-363, Jan., 1962. 1 fig., 13 refs.

149 (b). The Extent of the Adrenal Influence upon Renal Electrolyte Excretion in the Healthy Man on a Normal Diet, and Its Contribution to the Renal Changes on Standing
J. N. MILLS, S. THOMAS, and K. S. WILLIAMSON. *Journal of Endocrinology [J. Endocr.]* 23, 365-373, Jan., 1962. 3 figs., 21 refs.

In experiments here reported from the Department of Physiology of the University of Manchester spironolactone was given to 28 normal men and women at bedtime and on waking (200+100 mg. or 300+300 mg.) and its effect on the urinary excretion of sodium, potassium, and chloride measured at various times and under various conditions during the following day. Spironolactone itself tended to increase sodium and chloride excretion at night and also during the day while the subjects were lying down, standing up, and walking about. Potassium excretion was insignificantly reduced. Under all conditions the spironolactone treatment only partially inhibited the reduction in sodium excretion produced by an intravenous injection of cortisol (100 mg.) or aldosterone (250 μ g.); the effects on potassium excretion were less evident. Creatinine excretion rates were unaffected by the various procedures. The results are discussed in an attempt to assess the relative parts played by cortisol and aldosterone in the diurnal changes in electrolyte excretion and the changes produced on standing. It is concluded that "the low sodium excretion on standing is in part due to a non-adrenal, presumably haemodynamic factor; and in part to aldosterone secretion; and on standing there is a modest but significant fall in potassium excretion due to the non-adrenal factor". *Peter C. Williams*

150. The Different Effects of Aldosterone-like Steroids and Hydrocortisone-like Steroids on Urinary Excretion of Potassium and Acid

F. C. BARTTER and P. FOURMAN. *Metabolism: Clinical and Experimental [Metabolism]* 11, 6-20, Jan. [received March], 1962. 10 figs., 12 refs.

When aldosterone and other sodium-retaining steroids are administered, loss of potassium is among the well-documented sequelae. When ACTH and hydrocortisone and other carbohydrate-active steroids are administered, potassium loss also occurs. Studies were performed in man to determine whether the second type of potassium loss has a mechanism similar to that of the first. In balance studies it had been shown that the second type, as opposed to the first, regularly appears on the first day, seldom lasts more than a day even when treatment is continued, precedes sodium retention, is not prevented by sodium restriction or potassium administration, and precedes nitrogen loss. In short-term studies it was shown that the second type of potassium diuresis, as opposed to the first, may be accompanied by a rise of serum potassium. Whereas with aldosterone-like steroids there is an increase in urinary titratable acidity and ammonium with a fall of pH, with ACTH and hydrocortisone-like steroids there is usually a decrease in urinary titratable acidity and ammonium, with a rise of pH. Whereas the sodium-retaining steroids appear to promote exchange of potassium and hydrogen for sodium ions at the

renal tubular level, the carbohydrate-active steroids appear to release potassium from body cells, with the renal effects secondary thereto.—[Authors' summary.]

DIABETES MELLITUS

151. The Significance of the Renal Functional State in the Pathogenesis of Diabetic Glycosuria. (Значение функционального состояния почек в патогенезе диабетической глюкозурии)

L. I. ФОМИЧЕВА. *Проблемы Эндокринологии и Гормонотерапии [Probl. Endokr. Gormonoter.]* 8, 83-90, Jan.-Feb., 1962. 4 figs., 7 refs.

The occurrence of glycosuria in patients with diabetes mellitus depends not only on the degree of hyperglycaemia, but also on the functional state of the kidneys, as measured by the glomerular filtration rate and the rate of reabsorption by the tubules.

In the present interesting paper the results of investigations on 69 patients with diabetes mellitus of varying severity are reported. It is shown, for example, that in one patient with mild diabetes and a poor tubular reabsorption rate the urinary excretion of glucose (with a blood glucose level of 157 mg. per 100 ml.) was higher than in one with severe diabetes who had a blood glucose level of 249 mg. per 100 ml. but a high reabsorption rate. This second case, after successful resection of the stomach for post-ulcerative pyloric stenosis, developed a blood glucose level of 416 mg. per 100 ml. but remained aglycosuric, the tubular reabsorption rate having meanwhile risen to 719 ml. per minute. As a rule, the glomerular filtration rate was found to rise with the blood sugar concentration, and the reabsorption rate with the concentration of glucose in the filtrate; there was, however, no direct relationship. In the majority of the 69 patients the glomerular filtration rate was normal, but in 20% it was increased up to 180 ml. per minute. Concomitant diseases and threatened coma often lowered it considerably (to 47 ml. per minute or less).

It is concluded that absence or low levels of glycosuria in the presence of hyperglycaemia may be due to: (1) a lowered glomerular filtration rate resulting from arterial or cardiac disease, renal disease, or incipient coma; or (2) a raised tubular reabsorption rate, which, however, can take place only if the glomerular filtration rate is considerably increased. Conversely, a high level of glycosuria in the presence of slight hyperglycaemia may occur if the reabsorption rate is decreased to less than 90 mg. per minute, a situation which may occur in elderly persons or in patients whose capacity for phosphorylation of glucose is impaired, that is, a purely functional condition not related to true diabetes.

L. Firman-Edwards

152. The Functional State of the Kidneys in Diabetes Mellitus. (Функциональное состояние почек у больных сахарным диабетом)

А. Р. РАВЕНОВИЧ. *Проблемы Эндокринологии и Гормонотерапии [Probl. Endokr. Gormonoter.]* 8, 91-94, Jan.-Feb., 1962. 32 refs.

A study of renal function in 50 patients with diabetes showed that in 35 of them this function was impaired, as estimated by the glomerular filtration rate, blood urea level, and urea clearance. This impairment was not related

to the duration or severity of the diabetes, but was associated with insufficiently compensated metabolism. The glomerular filtration rate was lowered in 24 patients and raised in 18, in some of the latter fourfold. The tubular reabsorption rate was raised in 11 and slightly lowered in 4. The urea coefficient was raised in 28, but normal in 22. The urea clearance rate was lowered in 32 and normal in 18. More than one of these abnormalities often occurred in the same patient.

The presence of hyperglycaemia with slight or absent glycosuria was (as also shown by Fomicheva [see Abstract 151]) associated with a lowered glomerular filtration rate and also with low urea clearance which, in the author's view, was due to glomerulosclerosis. Yet in one patient with diabetes of 22 years' standing and diabetic retinopathy, renal function was normal. In addition to imperfectly compensated metabolism, other causes of renal dysfunction were inadequate treatment and the frequent occurrence of hypoglycaemic attacks.

L. Firman-Edwards

153. Alcohol Sensitivity in Diabetics Receiving Chlorpropamide

M. G. FITZGERALD, R. GADDIE, J. M. MALINS, and D. J. O'SULLIVAN. *Diabetes [Diabetes]* 11, 40-43, Jan.-Feb., 1962. 26 refs.

The authors report that flushing and other unpleasant side-effects are frequent when diabetic patients receiving chlorpropamide take alcoholic drinks. Conjunctival injection may be present and give the patient a "bull-eyed" appearance. Flushing begins 3 to 10 minutes after ingestion of even a small amount of ethyl alcohol and may be accompanied by a pounding headache and a feeling of breathlessness. It reaches maximal intensity in about 20 minutes and usually lasts about an hour. At the General Hospital, Birmingham, 100 consecutive diabetic-clinic patients taking 250 to 500 mg. of chlorpropamide daily were questioned. Of these, 35 had taken no alcohol since starting treatment, but of the remaining 65, 22 had experienced at least mild symptoms after taking alcohol. Many did not mention the reaction spontaneously, yet it was possible to confirm alcohol intolerance by giving a test dose. The clinical similarity of the phenomenon to that seen in chronic alcoholics receiving tetraethylthiuram disulphide (TETD) has suggested a similar pharmacological effect. It has thus been thought that chlorpropamide may block the oxidation of ethyl alcohol and cause an accumulation of acetaldehyde. Blood acetaldehyde estimations were therefore carried out on 4 patients taking chlorpropamide and who after being given 25 ml. of ethyl alcohol all showed toxic reactions. In none of these patients did the acetaldehyde levels approach those reported in alcoholic patients receiving TETD, and the ratio of acetaldehyde to ethyl alcohol was about 5 times less.

The authors point out that a large number of substances are known to cause facial flushing after ethyl alcohol. Apart from TETD, it is known that calcium cyanamide, the pyrazoline derivative irgapyrine, the vasodilator drug tolazoline, and furaltadone can all cause flushing after alcohol. It has also been shown that when liver slices are treated *in vitro* with ethyl alcohol and TETD there is an excessive accumulation of acetaldehyde, while a similar excess has been found at the height of the reaction produced by ethyl alcohol in animals receiving cyanamide, animal charcoal,

and irgapyrine. On the other hand, it has been pointed out that blood acetaldehyde levels after large quantities of ethyl alcohol may exceed those in patients treated with TETD, but that nevertheless flushing has not occurred.

The authors conclude that the TETD-alcohol reaction and the chlorpropamide-alcohol reaction are clinically similar. The commonly accepted explanation of the former does not apply to chlorpropamide and they suggest that the effect can be interpreted as an exaggeration of the normal response of a non-specific character of small blood vessels to ethyl alcohol. They stress that it is a common complication of chlorpropamide therapy and that a change to tolbutamide, with which such reactions are rare, is usually an effective method of dealing with the problem.

John Lister

154. The Incidence of Skin Reactivity to Insulin in Diabetic Patients

J. A. ARKINS, N. H. ENGBRING, and E. J. LENNON. *Journal of Allergy [J. Allergy]* 33, 69-72, Jan.-Feb., 1962. 4 refs.

At Marquette School of Medicine and Milwaukee County Hospital, Wisconsin, three groups of diabetics, totalling 148 patients, and one control group of 20 normal subjects were skin-tested with regular crystalline insulin. Of the diabetics who were receiving insulin, 53% gave a positive skin test result; of those who had previously taken insulin but not within the preceding year, 19% gave a positive reaction; while of the 29 diabetics who had never received insulin, only 3 showed a positive reaction. The control subjects all gave negative results. There was no positive correlation with age, duration of the diabetes, insulin dosage, history of local reactions, or allergic history.

H. Herxheimer

155. Absorption of Insulin- I^{131} from Subcutaneous Tissue in Diabetic Patients

M. C. BALODIMOS and R. H. WILLIAMS. *American Journal of the Medical Sciences [Amer. J. med. Sci.]* 243, 49-56, Jan., 1962. 3 figs., 10 refs.

The rate of absorption from subcutaneous tissue of insulin labelled with radioactive iodine (I^{131}) was studied at the University of Washington School of Medicine, Seattle, in healthy subjects and in 4 groups of diabetic patients. Protamine zinc insulin and crystalline insulin were iodinated with I^{131} and the rate of absorption was calculated from the rate of decrease of radiation from the site of injection. The authors made two important assumptions: (1) that the insulin is labelled homogeneously with an average of less than one atom of I^{131} per molecule of insulin, and (2) that the rate of disappearance of radioactivity from the injection site represented the rate of absorption of insulin, or in other words, that de-iodinization of the insulin- I^{131} did not occur to any considerable degree in the subcutaneous tissues at the site of injection.

The rate of disappearance of the labelled hormone was found to be higher in diabetics receiving insulin therapy regularly than in healthy subjects or in diabetics who had not received insulin regularly; the rate of absorption in the last two groups being similar. There was no apparent difference in the rate of absorption between diabetics receiving over 50 units of insulin daily and those receiving less than 50 units a day. Moreover, there was no significant difference in the rate of absorption between patients with lipodystrophy and unaffected patients.

R. E. Tunbridge

The Rheumatic Diseases

156 (a). Comparative Studies of Serologic Tests for Rheumatoid Disease. I. A Comparison of a Latex Test and Two Erythrocyte Agglutination Tests in a Random Population Sample

J. BALL, D. DE GRÁAFF, H. A. VALKENBURG, and F. W. BOERMA. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 55-60, Feb., 1962. 11 refs.

156 (b). Comparative Studies of Serologic Tests for Rheumatoid Disease. II. A Comparison of the Bentonite Flocculation Test and the Sensitized Sheep Cell Agglutination Test

J. BALL, K. J. BLOCH, T. A. BURCH, J. H. KELLGREN, J. S. LAWRENCE, and V. TSIGALIDOU. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 61-69, Feb., 1962. 15 refs.

The authors of these two papers from the Universities of Manchester, England, and of Leiden and Groningen, Netherlands, the National Institute of Arthritis and Metabolic Diseases, Bethesda, Maryland, and the British Empire Rheumatism Council's Field Unit set out to study the degree of correlation between different serological tests for rheumatoid disease as well as to determine the observer differences. In the first study sera from a random sample of the Rotterdam population consisting of 138 men and 135 women were examined by three tests—a latex-particle fixation test employing human F.II globulin was performed in Leiden; the sensitized sheep cell agglutination test (S.C.A.T.) in Manchester; and an agglutination test employing human erythrocytes with rabbit antihuman O-cell amboceptor in Groningen. Of the sera tested by these methods, 16, 13, and 17 respectively gave positive results, representing an over-all agreement of 93.3%. In each procedure an appreciable proportion of the positive results fell in a non-rheumatoid subgroup. The excess positive results in the first and third tests also fell in this group. It is deduced that the S.C.A.T. would give a significantly lower figure in a larger population sample.

The second comparison was made between the bentonite flocculation test (B.F.T.), performed at Bethesda, and the S.C.A.T., performed in Manchester. A first comparison was made on a random sample of 239 sera, of which 226 gave negative and 4 positive results in both tests, providing an agreement of 96%. A second clinical sample of 159 sera (that is, sera from patients with rheumatoid or other types of arthritis, collagen disease, or non-rheumatic diseases) was examined, in which agreement was obtained in 88%, 18 sera giving positive results with the B.F.T. and negative results with the S.C.A.T. on the single estimation. On 12 of these the S.C.A.T. was performed at other times, when 6 of them gave positive results. It is deduced that the B.F.T. "is a more sensitive indicator of potentially S.C.A.T. positive subjects than the S.C.A.T., especially if these subjects are clinically designated rheumatoid arthritis". It is also concluded that "in spite of the small proportion of discrepant results, it is difficult . . . to avoid the conclusion that they represent real serologic differences" and that "it would seem that the S.C.A.T. and F.II type tests cannot be regarded without reservation as interchangeable". Correlations with clinical and radiological features are set out. The

B.F.T. appears to be more sensitive than the S.C.A.T. in relation to the evidence of rheumatoid arthritis, but carries with it a lesser specificity.

Harry Coke

157. Pituitary and Adrenal Hormones in Rheumatoid Arthritis

O. SAVAGE, W. S. C. COPEMAN, L. CHAPMAN, M. V. WELLS, and B. L. J. TREADWELL. *Lancet* [Lancet] 1, 232-235, Feb. 3, 1962. 3 figs., 18 refs.

Since the therapeutic effects of adrenal corticosteroids in the treatment of rheumatoid arthritis are very similar to those of pituitary corticotrophin (ACTH) it has mistakenly been assumed that the pharmacological action and side-effects of the two series of hormones are much the same. In the present study the authors have observed 108 patients treated with oral steroids and 105 treated with ACTH over periods ranging up to 8 years at the West London Hospital. In their regimen these hormones are used only in cases which prove refractory to other forms of therapy, including gold and salicylates. They present a table which shows wide divergencies in the incidence of certain side-effects when the two hormone-treated groups are compared. Thus peptic ulceration and bruising were much more common with oral corticosteroids, whereas hypertension, acne, and skin pigmentation were more frequent with ACTH. By keeping the dosage of oral corticosteroids below the equivalent of 10 mg. of prednisolone daily, side-effects were reduced to a minimum; nevertheless bruising has become a most troublesome feature of prolonged oral steroid therapy. The use of alkaline-buffered oral preparations has reduced the incidence of dyspepsia. The authors found that the administration of ACTH could be stopped in one-quarter of their patients without causing serious withdrawal symptoms, whereas this was the case in only 3 of the 108 patients receiving oral corticosteroids.

In testing the reserve capacity of the pituitary to secrete ACTH they have used "metopirone" (SU 4885), a substance which stops the last stage of hydroxylation at the 11-steroid position so that Compound S is formed in the adrenal gland instead of cortisol. The former appears in the urine and can be estimated as 17-hydroxycorticosteroids (17-OHCS). Compound S does not suppress pituitary secretion as cortisol does, but causes a fall in cortisol production and this normally stimulates the pituitary to increase the output of ACTH, with a consequent increase in the adrenal steroid content of the urine; thus the output of adrenal steroids in the urine after metopirone can be used as a test of pituitary reserve. The authors applied this test with suitable precautions in case of withdrawal symptoms in 3 groups of patients. (I) To 17 patients receiving oral corticosteroids 40 units of ACTH was given for 4 days and the oral therapy discontinued. Then, after an interval of 60 hours metopirone in a dosage of 750 to 900 mg. was given orally 4-hourly for 24 to 72 hours. This produced a negative response which contrasted with the positive increase in 17-OHCS excretion in the urine after ACTH. Group II consisted of 12 patients receiving ACTH; all but one of these

gave a positive response after metopirone. Group III consisted of 19 patients with rheumatoid arthritis none of whom had received steroid therapy; here all gave a positive response to metopirone. These results show that the adrenal cortex still responds to stimulation by ACTH even after prolonged oral corticosteroid therapy. The pituitary gland does not respond to metopirone after prolonged oral corticosteroids, and the authors consider this reveals a difference in pituitary reserve which is in line with the other divergences between the two forms of hormone therapy.

William Hughes

158. **Anturan in the Treatment of Gout.** (L'anturan dans le traitement de la goutte)

J. LENG-LÉVY, J. DAVID-CHAUSSE, J. AUBERTIN, and M. LASSERRE. *Journal de médecine de Bordeaux et du Sud-Ouest [J. Méd. Bordeaux]* 139, 57-63, Jan., 1962. 3 figs.

This report from the Hôpital Saint-André, Bordeaux, describes the authors' experience with "anturan" (sulphinpyrazone) in the treatment of 22 cases of established and mostly severe gout. At first the drug was given in a daily dosage of 600 mg. but it was soon reduced to 200 to 300 mg.; as the "half-life" of anturan is only about 3 hours it is suggested that it should be given in divided doses 4 times a day. Any interruption of treatment may cause a prompt rise in the serum uric acid level and precipitate an acute attack of the gout. Among the side-effects are the possible deposition of urates in the urinary tract and recrudescence of gouty symptoms which, however, can be controlled by simultaneous administration of colchicine. Gastric intolerance (epigastric pain, diarrhoea, or vomiting) was noted in 6 of the cases, but yielded to interruption of treatment or reduction of dosage. None of the side-effects were serious and 17 of the patients benefited considerably. It is concluded that anturan is undoubtedly a new and valuable adjunct in the radical treatment of gout.

D. Preiskel

159. **Experience with Gout, with Particular Reference to Uricosuric Therapy with Anturan.** (Erfahrungen über die Gicht, insbesondere über die uricosurische Therapie mit Anturan)

C. H. MELLINGHOFF and R. H. GROSS. *Zeitschrift für Rheumaforschung [Z. Rheumaforsch.]* 21, 42-50, Feb., 1962. 3 figs., 32 refs.

The incidence of gout varies with the nutritional level of the particular population and accounts for 0.1 to 0.5% of all morbidity in countries with a high standard of living; 2 to 5% of "rheumatic diseases" are really manifestations of gout. This study, reported from Wuppertal-Elberfeld, is based on 30 cases of gout collected in the years 1956-61 (24 in men and 6 in women), of which 20 had been misdiagnosed at one time or another; thus in 13 cases the more or less typical gouty attacks were ascribed to acute rheumatism, while in 6 tophi had been overlooked. Altogether, tophi were present in 10 patients, renal calculi in 5, diabetes mellitus in another 5, and hypertension in 13.

Although satisfactory uricosuric effects had previously been obtained with probenecid, the dosage required tends to be too high and is often poorly tolerated. Since the beginning of 1961 the authors have used "anturan" (sulphinpyrazone) which can be given in smaller dosage. In 7 out of 8 cases the serum uric acid levels (initially 7.0 to 16.4 mg. per 100 ml.) returned to normal in 1 to 8 days, but in

the remaining case treated with probenecid for several months, the result was disappointing. Initial large doses of anturan may precipitate an attack of gout, which can be controlled by simultaneous administration of phenylbutazone, but it may be preferable to start with a dose of 100 to 200 mg. daily, given morning and evening. Anturan must be continued for long periods without interruption, but the maintenance dose has to be individually determined and adjusted according to the serum uric acid level. The drug is usually well tolerated and there were no attacks of gout while it was being given. In one patient with hypercholesterolaemia the serum cholesterol level fell *pari passu* with the serum uric acid level. This observation had been noted by other workers, but still awaits a satisfactory explanation.

D. Preiskel

160. **Scleroderma and Its Relationship to the "Collagenoses": Dermatomyositis, Lupus Erythematosus, Rheumatoid Arthritis and Sjögren's Syndrome**

D. L. TUFFANELLI and R. K. WINKELMANN. *American Journal of the Medical Sciences [Amer. J. med. Sci.]* 243, 133-146, Feb., 1962. Bibliography.

The authors have studied the incidence of other collagen diseases and/or autoimmune processes in 727 cases of systemic scleroderma seen at the Mayo Clinic between 1935 and 1958. Of the 727 patients 36, 27 of them females, showed features of dermatomyositis. Seven out of 9 had a raised serum transaminase level, 8 out of 10 positive muscle biopsies, and in 18 out of 20 the electromyogram showed myositis. Pulmonary fibrosis occurred in 6 cases. Five cases were positive to the L.E.-cell test. In 3 the additional diagnosis of Sjögren's syndrome and/or systemic lupus erythematosus was made, and one also had hepatic cirrhosis. Clinical features of rheumatoid arthritis were present in 31 cases (29 female) and 7 of these had fibrosis of the lung. Seven women had Sjögren's syndrome and one Hashimoto's thyroiditis. The albumin:globulin ratio was reversed in about 20% of patients, and a false (biological) positive reaction for syphilis was found in 10.

The authors suggest that these results support the view that some cases of scleroderma are due to autoimmune processes.

G. L. Asherson

161. **Successful Treatment of Three Cases of Scleroderma with Vitamin D₂.** (Успешное лечение витамином D₂ трех больных склеродермией)

S. JU. ALIBEKOV and H. M. HALILOV. *Вестник Дерматологии и Венерологии [Vestn. Derm. Vener.]* 36, 69-71, Feb., 1962.

The authors have treated 3 patients, 2 with local circumscribed scleroderma and one with the generalized form of the disease, with vitamin D₂ (calciferol), with good results. Several courses of treatment were given to each patient, the dosage ranging between 3 and 15 million units of the vitamin per course. Physiotherapy was given concurrently with the vitamin, and the courses of vitamin therapy were repeated as relapses occurred.

N. Hopewell

162. **The Visceral Manifestations of Scleroderma.** [Review Article]

M. A. SACKNER. *Arthritis and Rheumatism [Arthr. and Rheum.]* 5, 184-194, April, 1962. 1 fig., bibliography.

Psychiatry

163. The Character Structure of Sex Offenders

S. B. KÖPP. *American Journal of Psychotherapy* [Amer. J. Psychother.] 16, 64-70, Jan., 1962. 4 refs.

This paper summarizes the author's clinical impressions gained at New Jersey State Hospital, Trenton, N.J., from a study of over 100 male sex offenders, to approximately half of whom he gave group or individual therapy, or both, for periods up to 2½ years. He concludes that among sane but compulsive sex offenders two contrasting character types occur. (1) The neurotic, who experiences his offence as an alien occurrence, not part of his normal self. Thus, the neurotic exhibitionist is generally shy, passive, and overtly conscientious; regards his offence as shameful, and tries to disown it by saying it just "came over" him. (2) The man with a character disorder rationalizes his acts in terms of the sort of person he thinks he is. This type forms a minority among exhibitionists. He is loud, brash, openly seeks attention, and tends to rationalize his exposure as a sexual invitation. Both types have a similar basic resentment of domination by women and a need to turn the tables by shocking them.

A similar division runs through other types of sex offenders. Among paedophiles, there is the active, superficially successful man-of-the-world, who can only admit his offence with great shame and as an isolated incident foreign to his usual self. In contrast, the child-like type of immature character, who is not at ease with his own age group, may rationalize his relationships with prepubescent girls as romances. Both types, unconsciously, see sex as aggressive and fear the retaliation of the adult woman. Among rapists there is a typically predatory character deviant with the attitude of "I want it so I take it", whether it be money or sex. In contrast, the normally over-compliant person, who spends a lot of time trying to please without always succeeding, may have an aberrant outburst, as with the man who assaulted a woman saying "now you are going to satisfy me". Afterwards he feels very guilty and concerned to make amends to his victim. Psychodynamically, both types feel a need to steal love.

These two types of sex offenders require different psychotherapeutic methods. A group which includes both types works well, since the one readily detects the underlying hypocrisy of the other's defences. D. J. West

164. Recent Critical Trends in Mental Hospital Admissions in the Oxford Region

A. BARR, D. GOLDING, and R. W. PARNELL. *Journal of Mental Science* [J. ment. Sci.] 108, 59-67, Jan. [received March], 1962. 1 fig., 8 refs.

Between 1954 and 1958 [in mental hospitals in the area of the Oxford Regional Hospital Board] male admissions increased 29%, re-admissions increased 56%; female admissions increased 50%, re-admissions increased 70%. In the same time the resident mental hospital population decreased by 10%. The number of first admissions for schizophrenia changed little. This was also true for disorders of character, behaviour and intelligence. An increase

in proportion of women patients, and of male re-admissions, were discharged within 6 months. On the other hand men admitted for the first time in 1958 stayed in hospital just as long as in 1954, and no reduction can be seen in the proportion staying more than 12 months. The greatest reduction in time spent in hospital was among schizophrenics. For male first admissions the median stay was reduced from 4.13 to 2.7 months. Larger reductions were found for male re-admissions and for women.

Compared with London from 1947 to 1951 (Norris, 1957) and with Buckinghamshire in 1933 and 1947 (Shepherd, 1957) there is a remarkable reduction in the proportions of longer stay patients with both schizophrenia and affective disorders. The median duration of stay has now reached a critical level with regard to the need for hospital accommodation. The implications of this are discussed.—[Authors' summary.]

165. The Psychopathology of Inflammatory Disease of the Brain in Childhood. (Die Psychopathologie der entzündlichen Hirnschädigung im Kindesalter)

A.-L. ANNELL. *Acta paedopsychiatrica* [Acta paedopsychiat.] 29, 7-21, Jan., 1962. 21 refs.

The author discusses her observations on post-encephalitic patients at the University Psychiatric Clinic for Children and Adolescents at Uppsala. The introduction of sulpha drugs and antibiotics has changed the clinical manifestations and outcome of encephalitic infections which occur prenatally or during the first year of life. It has also been realized recently that certain varieties of encephalitis can appear as mild diseases in which psychiatric symptoms may play a predominant part. As examples are quoted toxoplasmosis, *Listeria* infection, infectious mononucleosis, Asiatic influenza, and some forms of E.C.H.O. virus meningitis.

The post-encephalitic sequelae are often only temporary, lasting perhaps for a couple of years. They are primarily due to organic brain defects and functional changes. The child's intellectual and emotional development is handicapped by them in a way for which he is not responsible. He may, however, be criticized for educational failures and poor achievement in all tasks requiring agility and good coordination. Such criticism may be resented and thus give rise to secondary sequelae in the form of behaviour disorders which are often wrongly diagnosed as due to psychopathy or mental deficiency.

Among the primary sequelae were found: (1) motor disturbances, such as mild forms of spasticity, Parkinsonism, or poor coordination; (2) speech disturbances, such as stammer, aphasia, dyslexia, dysgraphia, and acalculia; (3) epileptic manifestations, such as petit mal, twilight states, tics, increased irritability, periodic vomiting, and headaches of migraine character; (4) disturbances of perception and ideation, revealing themselves especially in poor performance in relevant tests; (5) disturbances of affect and impulse, such as hyperactivity and explosive outbursts; and (6) psychotic symptoms, such as visual and somatic hallucinations and unpredictable behaviour.

Many primary sequelae respond well to suitable medication directed against spasticity, Parkinsonism, or epileptic phenomena. Secondary sequelae of a psychogenic nature can be reduced by informing parents and teachers of the organic basis of the child's difficulties. They may be largely prevented by a judicious educational programme.

F. K. Taylor

166. Suicide and Suicidal Attempts in Children and Adolescents

J. M. TOOLAN. *American Journal of Psychiatry* [Amer. J. Psychiat.] 118, 719-724, Feb., 1962. 10 refs.

It is pointed out that both attempted and completed suicide are commoner in childhood and adolescence than is generally held to be the case, and in this paper from Bellevue Hospital, New York, figures are cited in support of this contention. From an examination of 102 children under 16 presenting with suicidal thoughts and actions the author reaches the conclusion that depression is an important factor.

White children commit suicide more frequently than negroes, boys complete suicide more frequently than girls, who make more attempts, and there is a high rate of suicide among the Puerto Rican population in New York, which explains the unusually high rate in Roman Catholics. Puerto Rican youngsters in New York are very liable to choose suicide as a method of solving problems. The number of juvenile suicides in broken homes is high, and even when parents are living together there is often a state of emotional disorganization. The author considers that depression frequently occurs in childhood but that symptoms differ from those in the adult. Tantrums, truancy, accident proneness, and masochistic behaviour often indicate childhood depression.

Loss of the love object is the common denominator in all depressive reactions and most of the children in the author's series were deprived of one or both parents. The paradox that the more neglected the child, the more he needs his parents is described, and the psychopathology of depressive reactions turning against the child himself is examined. The author points out that a child under 10 has an incomplete "notion" of death; he considers "it reversible and seldom if ever applicable to himself", which explains the low suicide liability in the very young.

Gavin Thurston

167. Guilt, Pain, and Success: Success Facilitated by the Pain of Glomus Tumor and Peptic Ulcer

G. L. ENGEL. *Psychosomatic Medicine* [Psychosom. Med.] 24, 37-48, Jan.-Feb., 1962. 11 refs.

The author of this paper from the University of Rochester Medical Center, New York, describes a single case illustrating the part played by guilt and pain in promoting personal advancement. Full clinical details are given.

Psychiatric examination of a 48-year-old man who had been singularly successful in the business world disclosed that he had suffered from a duodenal ulcer since he was 20 and from a glomus tumour of the toe since he was 21. Adequate surgical treatment of both conditions was followed by a marked decline in health and in the pattern of success, and the patient began to indulge excessively in alcohol. A subsequent follow-up inquiry revealed that after sustaining a head injury he had deteriorated intellectually and that eventually he ceased to display his customary aggressive hyperactivity.

It is considered that in this patient an unconscious sense of guilt deriving from childhood experiences functioned as a powerful motivating force towards success. In early life he had strenuously attempted to emulate an unusually exacting father. The author suggests that this case raises theoretical questions concerning the impact of surgical treatment upon personality adjustment.

A. Balfour Sclare

168. Treatment of Anxiety States by Antidepressant Drugs

W. SARGANT and P. DALLY. *British Medical Journal* [Brit. med. J.] 1, 6-9, Jan. 6, 1962. 10 refs.

The authors report from St. Thomas's Hospital, London, the results obtained with monoamine oxidase (MAO) inhibitors given either with or without chlördiazepoxide in the treatment of 60 cases of "atypical" depression, that is, cases in which hysterical, phobic, obsessional, or anxiety symptoms (particularly the last) were prominent. Three groups are considered on the basis of their response: (1) those responding to MAO inhibitors alone, (2) those responding to these drugs plus chlördiazepoxide, and (3) those not responding to MAO inhibitors and only slightly to chlördiazepoxide.

A higher percentage of the 15 patients in Group 1 had the following characteristics, compared with the 17 in Group 3: good previous personality (87% and 29% respectively), precipitating factors (73% and 23%), felt worse in the morning (60% and 6%). A higher percentage of those not responding (Group 3) blamed others for their troubles (65% compared with 13% in Group 1), while none in this group blamed themselves, compared with 27% in Group 1. Factors such as age, length of illness, family history, past breakdowns, and presence of anxiety or hysteria did not appear related to response. [However, the number of cases in each group was very small and the results were not tested for significance. The various groups and categories are based on clinical impression, so that the results can only be regarded as indicating possible trends.]

The authors conclude that MAO inhibitors are more effective in atypical depression with anxiety in those patients whose previous personality was good. The possibility arises that the action of these drugs may be against anxiety and in stabilizing the autonomic nervous system rather than as a specific antidepressant. In conclusion they emphasize that the patients must be warned that no good effect can be expected for 4 to 8 days and that side-effects may occur. The maintenance dosage should be carefully regulated in order to avoid relapse. If this does occur on withdrawal of the drug the latter may be given in full dosage, returning as quickly as possible to maintenance levels.

Christopher Wardle

169. The Self-referent Attitudes of Neurotic and Inadequate Personalities

A. B. MONRO. *Journal of Mental Science* [J. ment. Sci.] 108, 37-46, Jan. [received March], 1962. 14 refs.

This paper deals with the self-referent attitudes found in a characteristic sample population of non-psychotic patients in mental hospitals. The method of choosing the sample is described, based on figures derived from England and Wales, and New Zealand. A list of self-referent traits is set out, derived from the writer's modification of Cattell's comprehensive trait list, published in 1946. Each trait selected for use in this paper is provided with an operational definition:

The table of tetrachoric correlation coefficients between each trait and every other trait, for the sample population of 150, is set out. From this table 22 correlation clusters are derived, each constituent trait correlating with every other trait to the extent of +0.50 (with certain minor, specified exceptions). These clusters are found to form two important nuclei, one of which appears to denote uncritical acceptance of under-valuation of the self; the other appears to be characterized by rejection of under-valuation. Some of the other clusters describe well-known psychiatric syndromes; some, however, though clear and unambiguous, require further investigation before interpretation can be attempted. These findings are a possible stimulus to psychotherapeutic invention.—[Author's summary.]

170. The Abnormality of Tryptophan Metabolism in Children with Mongolism

D. O'BRIEN and A. GROSHK. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 17-20, Feb., 1962. 2 figs., 16 refs.

The work of previous authors has suggested that a defect of tryptophan metabolism exists in children with mongolism. In the study reported here from the University of Colorado Medical Center, Denver, and the Colorado State Home and Training School, Wheatridge, Colorado, the nature of the defect was investigated by examining the urinary metabolites of tryptophan after its administration to mongoloid and other children. The subjects consisted of 21 mongols (aged 9 to 16 years) and 19 non-mongoloid mental defectives of comparable age, sex, and intelligence. The experiments were conducted by feeding 100 mg. L-tryptophan per kg. body weight to the fasting subjects and collecting the urine for the next 7 hours. The urine samples were assayed for 5-hydroxy-indolylacetic acid and for the following metabolites of the pathway from tryptophan to nicotinamide: kynurenine, kynurenic acid, 3-hydroxy-kynurenine, xanthurenic acid, 3-hydroxyxanthurenic acid, N-acetyl-kynurenine, and N-methylnicotinamide. The content of 4-pyridoxic acid was also determined, as vitamin B₆ is involved in the pathway.

The mongoloid children excreted less of all the metabolites of the kynurenine pathway, but the difference from the control group was only significant ($P < 0.01$) in the case of xanthurenic acid. No differences were detected in the excretion of 5-hydroxyindolylacetic acid or 4-pyridoxic acid. Determination of serum tryptophan levels showed there was no marked defect in the absorption of tryptophan from the intestine in the mongoloid children. The authors consider that their results suggest that an abnormality of the hydroxy-kynurenine transaminase system with a resulting impairment of the conversion of 3-hydroxykynurenine to xanthurenic acid is present in the mongoloid children examined. They admit, however, that they have not excluded abnormalities in the renal clearance of xanthurenic acid in their subjects.

R. Rodnight

171. Amphetamine Addiction

D. S. BELL and W. H. TRETHOWAN. *Journal of Nervous and Mental Disease* [J. nerv. ment. Dis.] 133, 489-496, Dec., 1961 [received March, 1962]. 38 refs.

A series of 14 patients (8 male and 6 female, aged 26 to 49 years, average 33 years) admitted to hospital on account of psychotic episodes apparently associated with amphet-

amine addiction are reviewed in this paper from the New South Wales Division of Mental Hygiene and the University of Sydney. In addition to amphetamine sulphate, drugs of addiction were dextroamphetamine, methylamphetamine, and "preludin". Of the 14 patients 11 had been addicted for more than 3 years. The daily intake varied widely, the average being probably around 200 mg., but in one case it reached 1,000 mg. Most of the patients periodically took alcohol and/or other drugs (caffeine, barbiturates, bromides, and, in one case, morphine) to excess.

All the patients showed evidence of underlying personality instability, neurotic or pre-psychotic, but there was no common pattern. All had had a disturbed childhood and there was an unfortunate family history in all cases. Overt mental illness had occurred in 7 families, alcohol or drug addiction in 6, and suicide in 2. Sexual adjustment was poor in all cases (of the 10 married patients, 3 were divorced and 6 were separated). The commonest personality defect seems to have been a passive-receptive form of mastery. The effects desired from the drug could be described as mental stimulation, the patient feeling that he could "do (or master) anything". Subjective impressions of heightened intellectual activity were often accompanied by objective signs of improved performance, but the increase in libidinal drive resulted in disturbances of equilibrium, breakdown of defences, and regression.

Withdrawal symptoms were limited to depression, physical symptoms being few and unimportant. No form of treatment proved very effective. The relapse rate was high (the 14 patients were admitted to hospital on at least 25 separate occasions), and continued addiction was the rule, leading to a gradual deterioration in working, social, and home life.

Rex Matthews

AFFECTIVE DISORDERS

172. Drug Therapy in Depressions—Controlled Evaluation of Imipramine, Isocarboxazide, Dextroamphetamine-amobarbital, and Placebo

J. E. OVERALL, L. E. HOLLISTER, A. D. POKORNY, J. F. CASEY, and G. KATZ. *Clinical Pharmacology and Therapeutics* [Clin. Pharmacol. Ther.] 3, 16-22, Jan.-Feb., 1962. 1 fig., 14 refs.

The authors summarize their paper as follows. "An evaluation of imipramine, isocarboxazide, dextroamphetamine-amobarbital, and placebo was carried out in 204 patients with depressive syndromes in thirty-two Veterans Administration Hospitals. Treatment with a fixed dosage schedule was followed for 3 weeks, the dosage becoming flexible during an ensuing 9 week period. Evaluation of responses was made by three rating scales specially derived for depressed patients.

"After 3 weeks of treatment, imipramine was significantly more effective than the other three treatments as measured by a thirty-one item expert clinician's scale derived from the Inpatient Multidimensional Psychiatric Scale. Favorable responses to imipramine were often prompt, leading to loss of such patients from the study before the full 12 week treatment period had been completed. After 12 weeks of treatment, the patients who remained in all four treatment groups were significantly improved when each group was compared with its pretreatment level, but there were no

statistically reliable differences between treatments at the end of the study."

The authors conclude that imipramine is clearly the drug of choice for treating depressed patients, though related drugs might possess equal or greater efficacy. They emphasize the need for controlled trials in the evaluation of psychopharmacology, particularly in the treatment of depression. Whenever a clinical symptom, such as depression, shows a strong tendency to spontaneous remission, a placebo control is necessary.

J. MacD. Holmes

173. The Clinical Manifestations of Depressive Illness with Abnormal Acetyl Methyl Carbinol Metabolism

W. McC. ANDERSON and J. DAWSON. *Journal of Mental Science [J. ment. Sci.]* 108, 80-87, Jan. [received March], 1962. 3 figs., 8 refs.

In this work from Runwell Hospital, Essex, the authors studied the blood acetyl methyl carbinol (A.M.C.) levels in patients suffering from depression. The clinical and biochemical assessments were carried out independently. The series consisted of 98 patients (20 men and 78 women). The A.M.C. content of three consecutive morning specimens of fasting blood were estimated.

Irrespective of clinical diagnostic categories of depression it was found that the blood A.M.C. levels paralleled the depressive symptoms—retardation (R) and depressive pre-occupation (P). Thus high blood A.M.C. levels (above 50 μ g. per 100 ml.) were found in 32 of the 42 patients having a high (R+P) score and a low blood A.M.C. level was found in 40 of the 56 patients with low (R+P) scores.

The authors put forth a hypothesis connecting biochemical changes affecting the neural functions and those causing affective disorders.

N. Rathod

174. Etryptamine Acetate—a New Antidepressant Chemical
T. R. ROBE. *Journal of Neuropsychiatry [J. Neuropsychiat.]* 3, 181-185, Feb., 1962. 8 refs.

The use of iproniazid and other monoamine oxidase inhibitors in the treatment of depression is sometimes followed by side-effects such as liver damage, hypotension, oedema, insomnia, skin rashes, impotence, and peripheral neuritis. The present author reports the results of treatment of 98 depressed patients with etryptamine acetate ("monase"). Severe toxic effects were not observed—the absence of liver damage and severe hypotension is commented on particularly by the author. While no controls were used, 51 of the 98 patients did "well" or "very well". While the exact mode of action of these antidepressant drugs is not known, there is evidence that they now have a place in the treatment of depressive illnesses.

B. M. Davies

175. Treatment of Facial and Head Pain Associated with Depression

H. E. WEBB and R. G. LASCELLES. *Lancet [Lancet]* 1, 355-356, Feb. 17, 1962.

Commenting that "too little attention is being paid... to the depressive aspect of chronic pain", the authors of this paper from St. Thomas's Hospital, London, report the use of antidepressant drugs in cases of pain in the facial region and neck associated with depressive symptoms. Two groups of patients were treated. Group I consisted of 21 patients with pain of organic type corresponding to the anatomical distribution of the fifth cranial nerve, and Group II of 10

patients whose pain did not suggest any organic origin. A number of these patients had symptoms associated with a true endogenous depression, as indicated by early waking and daily mood swings, but this picture was by no means typical. Many had mild obsessional signs such as excessive tidiness. The chief drug used was phenelzine ("nardil") in a dosage of 15 mg. 3 or 4 times a day; and in some cases imipramine ("tofranil"), 25 to 50 mg. thrice daily, was added or substituted. The effect of this treatment in relieving pain as well as in alleviating the underlying depression appears to have been dramatic. Only 4 patients from Group I and 2 from Group II failed to obtain relief. Summaries of 2 cases from each group are given, in all of which the patient had complete relief from pain.

E. H. Johnson

SCHIZOPHRENIA

176. Massive Niacin Treatment in Schizophrenia: Review of a Nine-year Study

H. OSMOND and A. HOFFER. *Lancet [Lancet]* 1, 316-320, Feb. 10, 1962. 11 refs.

It has been suggested (Osmond and Smythies, *J. ment. Sci.*, 1952, 98, 309) that schizophrenia may be caused by a deviant metabolite of adrenaline. The present authors consider that on this assumption any substance which reduces adrenaline production should ameliorate the illness, and they selected niacin in the hope that by competing for methyl groups it would "prevent more noradrenaline being methylated to adrenaline".

Encouraged by the favourable results of an initial double-blind trial, they carried out a more extensive investigation covering all patients treated for schizophrenia in Saskatchewan between 1952 and 1955. Altogether 73 patients received niacin in hospital, 13 of whom continued this treatment for varying periods, and 98 patients received other treatment. During the period under review there were 7 readmissions in the niacin group and 47 among those not receiving niacin. Over the next 4 years (1956-9) the readmission rate in the niacin-treated group slightly exceeded that in the controls, but the over-all frequency and duration of readmission was still substantially less. Within 5 years of discharge half the patients not receiving niacin had been readmitted at least once, compared with only one-sixth of those receiving this drug. Nevertheless it seems that many schizophrenics may require intermittent or even continuous treatment over many years.

In a prospective study, 82 patients who completed a second double-blind trial were followed up for 3 to 7 years. A 5-year cure was obtained by 55% of the patients who received niacin in hospital and for at least one year after discharge, compared with only 20% of those receiving standard treatments. The value of long-term assessment was especially evident when, to exclude the possible influence of therapeutic enthusiasm, the authors studied the course of patients who had received niacin in hospital "from doctors who were disinterested, or even sceptical, about its efficacy". While there was little difference at the time of discharge, nearly 5 years later the niacin-treated group showed a clear advantage over those who had received electric convulsion therapy (E.C.T.) only. The authors briefly refer to studies by two independent workers, one of whom obtained an immediately beneficial effect with niacin

while the other found that the drug was of little help in chronic regressed schizophrenics.

Discussing treatment the authors state that in out-patients 3 to 6 g. of niacin or its amide is given daily at the start; if there is improvement in 3 months this dosage is continued for a year and then the drug is withdrawn. If there is a relapse further treatment is given for 5 years, either intermittently or continuously. An out-patient who fails to improve in 3 months should be admitted to hospital for other treatment, including E.C.T. Niacin produces a flush, but nicotinamide does not; the flush, however, is well tolerated. No serious toxicity or side-effects were noted in the present series. The authors enter a plea for large-scale assessment of niacin. Although it remains an empirical remedy and has definite therapeutic limitations it also possesses distinct advantages: it is cheap, safe, and can easily be given for years on end. These and the clinical benefits to be derived from niacin have been virtually ignored and some possible reasons for this are discussed.

Alan A. Black

177. Insulin Treatment of Schizophrenia: a Three-year Follow-up of a Controlled Study

B. ACKNER and A. J. OLDMAN. *Lancet* [*Lancet*] 1, 504-506, March 10, 1962. 4 refs.

A previous paper (Ackner *et al.*, *Lancet*, 1957, 1, 607; *Abstr. Wld Med.*, 1957, 22, 139) described a controlled trial at Bethlem Royal Hospital, London, and Cane Hill Hospital, Coulsdon, Surrey, in which 50 patients with a history of schizophrenia of under one year's duration were randomized by age and diagnostic subtype and allocated to coma treatment with either insulin or barbiturates by mouth, the treatment regimen being otherwise similar in the two groups. Six months later little difference was observed in the clinical and social status of the patients whether coma had been induced with insulin or barbiturates. This assessment, like subsequent ones, was made at an interview in the absence of any knowledge of the actual treatment given. Clinical status was classified as recovered, residual defect, or psychotic symptoms still present, and social status as independent, socially dependent, or in hospital.

The present authors describe the condition of these 50 patients, and of 16 others similarly treated, at follow-up interview 12 months, 2 years, and 3 years after treatment. They point out that if the results are presented cumulatively, as has been done in other studies, the effects of treatment may be masked by the inclusion of patients who later improved spontaneously. To minimize this, the outcome at 6 months was taken as reflecting the treatment response and patients in each of these "outcome categories" were followed up separately. Analysed in this way, the results showed that of 15 insulin-treated patients who recovered at 6 months, 8 required 13 readmissions during the next 2½ years, whereas only one of the 12 recovered controls was readmitted. Of patients considered recovered or independent at 6 months, those treated with insulin subsequently had longer periods of psychosis and of stay in hospital than controls. The 3-year follow-up therefore provided no evidence in favour of insulin-coma treatment.

Although the number of patients (66) was small compared with previous investigations the authors claim that their series was more carefully selected and controlled, the assessments being reached without knowledge of the treatment given.

Alan A. Black

178. Autistic Schizophrenic Children: an Experiment in the Use of D-Lysergic Acid Diethylamide (LSD-25)

A. M. FREEDMAN, E. V. EBIN, and E. A. WILSON. *Archives of General Psychiatry* [*Arch. gen. Psychiat.*] 6, 203-213, March, 1962. 14 refs.

The efficacy of D-lysergic acid diethylamide (LSD-25) in adult neurotic patients is uncertain, and in adult schizophrenia tolerance is developed after 3 doses in those few cases where any effect is demonstrable; the authors of this paper from New York Medical College could find only 5 references to its use in children.

Twelve children were studied, ranging in age from 5 years 11 months to 11 years 10 months; all were autistic, attending a day school for schizophrenic children; 7 were mute and 5 were almost silent. Ten of the children received 100 mg. of LSD-25, one received 50 mg., and one had 110 mg. on one occasion and 200 mg. on another. LSD-25 was given orally in a liquid vehicle which the children liked. The children were observed by a "pediatric psychiatrist" from the time of administration until the effects appeared to have worn off.

The onset of effects occurred on average 20 minutes after administration and lasted on average 4 hours 10 minutes. Pupillary dilatation occurred in all subjects, facial flushing in 11, ataxia in 5, catatonic posturing in 3, and relaxed or "doughy" muscle tone in 7; stroking and other movements suggested increased awareness of a part of the body in 8; 6 of the children seemed to desire more than usual physical contact with the staff. Extreme and rapid mood changes were observed, particularly euphoria (11 cases) and anxiety (7 cases). Hallucinations seemed to be experienced by 7 children. There appeared no consistent change in alertness or contact with the environment. Those children who already talked did so more freely, but without using any new vocabulary; none of the mute children spoke.

[This uncontrolled descriptive study suggests that LSD-25 is of no value in the treatment of autistic children.]

Christopher Wardle

179. Effects of LSD-25 on Relatives of Schizophrenic Patients

G. ANASTASOPOULOS and H. PROTHADES. *Journal of Mental Science* [*J. ment. Sci.*] 108, 95-98, Jan. [received March], 1962. 5 figs.

This paper from the Aristotle University of Thessaloniki, Greece, describes an attempt to determine whether the relatives of schizophrenic patients would show symptoms common to the patients when given D-lysergic acid diethylamide (LSD-25); 20 families of such patients were studied, of which 4 had a family history of schizophrenia and 2 a healthy mental history. LSD-25 was given orally in doses of 1 or 1.5 µg. per kg. body weight.

Manifest differences in reactions were revealed amongst the relatives of schizophrenics as compared with healthy people, the most important being (a) that the relatives of the schizophrenic patients misinterpreted intoxication experiences and also the immediate environment and showed ideas of reference; and (b) that these relatives expressed feelings of loss of external reality and also of severe depression, fears of having become mad, and that this was purposely induced and would be permanent. The reactions were also of longer duration than were those in the members of "normal" families.

N. Rathod

Paediatrics

PREMATURITY AND NEONATAL DISORDERS.

180. The Syndrome of Late Jaundice with Pulmonary Disease in the Premature Infant. (Le syndrome ictère tardif-pneumopathie du prématuré)

P. MONNET and J. TOURNIAIRE. *Archives françaises de pédiatrie* [Arch. franç. Pédiat.] 18, 1014-1025, Sept., 1961 received Feb., 1962]. 13 refs.

Jaundice of late onset in premature infants is a recognized entity of variable aetiology; occasionally it may form part of the syndrome described by Rossier *et al.* (Arch. franç. Pédiat., 1958, 15, 477) in which there are accompanying respiratory difficulties and bone changes, and 3 such cases are described in detail in this paper from the Hôpital Debrousse, Lyons. The infants weighed only 1,700, 1,300, and 1,200 g. respectively at birth. In 2 cases the jaundice appeared on the 47th and 83rd days of life respectively and lasted one to 2 months; but no jaundice occurred in the third case, although hepatosplenomegaly was present and tests showed disturbance of liver function. Respiratory difficulties were present in all 3 infants; these started between the 1st and 2nd months and lasted from 10 days to almost a year. The radiological changes observed in the lungs were non-specific.

[In the absence of any bone changes it is difficult to understand how these cases can be included in the syndrome as the authors claim.]

David Morris

181. Clinical Observations in Newborn Premature Infants

R. L. CORT. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 53-62, Feb., 1962. 3 figs., 16 refs.

In this detailed study of 155 premature infants under observation at the Institute for the Care of Mother and Child, Prague, information was collected on weight loss, body temperature, and regurgitation. The infants' birth weight ranged between 1,000 and 2,500 g. and the over-all mortality was 18.7%, deaths occurring mainly within the first 3 days: the infants dying within 24 hours of birth tended to be smaller (average weight 1,187 g.) than those dying after 24 hours (average weight 1,506 g.). A poor prognosis was associated with a preceding premature twin, maternal metabolic diseases, birth complications, caesarean section, delay in the onset of breathing, and, to a slight extent, primiparity. Toxaemia (which the author states was rare, presumably because of differences in the concept and definition of the condition), stained amniotic fluid, and working mothers seemed to make no difference to the outcome. The incidence of regurgitation was studied in a group of 80 infants of an average birth weight of 2,102 g.; this significantly influenced weight loss and seemed to affect the more immature infants. Regurgitation occurring within 12 hours of birth and before feeding was started was regarded as abnormal; sedation and tube feeding tended to reduce the incidence of regurgitation. In a study of the weight loss, which was variable, the presence of clinical oedema was not always associated with large weight loss, [though it appears from the material presented that large weight loss suddenly after

birth may be due to loss of oedema fluid]. The incidence of clinical respiratory or neurological illness, which decreased with maturity, appeared to be associated with low body temperature, but the author's use of chlorpromazine makes this difficult to evaluate.

David Morris

182. Idiopathic Cholestasis in the Neonatal Period

H. STEIN and C. ISAACSON. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 63-67, Feb., 1962. 6 figs., 7 refs.

Whereas bile stasis in the first 3 months of life is usually associated with bile-duct atresia or such disorders as galactosaemia or hepatitis, it can occur idiopathically as a biochemical dysfunction of the liver cells. This is well illustrated in this paper from the Baragwanath Hospital, Johannesburg, in which such a condition in 4 premature Bantu children is described in detail. Their birth weights were between 3 lb. 12 oz. (1,700 g.) and 5 lb. (2,268 g.). Jaundice, which was at least partially obstructive, first appeared between 12 and 28 days with serum bilirubin levels between 5.7 and 22.5 mg. per 100 ml. All 4 children died within 10 days of the onset of the jaundice, and on microscopical examination of the liver there was marked bile stasis either in the centrilobular or centrilobular regions, with bile plugs in the canaliculi, but no evidence of hepatitis. The differential diagnosis of an intermittent obstructive jaundice presenting between 12 and 28 days in the absence of haemolytic disease or other demonstrable disorders would seem to rest between neonatal hepatitis and bile stasis. The possibility that the stasis could be a manifestation of hepatitis without microscopical changes in the liver is also discussed.

David Morris

183. Oxygen Consumption in Newborn Premature Infants

H. C. MILLER, F. C. BEHRLE, J. L. NIEMAN, R. DRIVER, and B. A. DUDGING. *American Journal of Diseases of Children* [Amer. J. Dis. Childh.] 103, 39-46, Jan., 1962. 4 figs., 14 refs.

184. Hemolysis as a Contributing Factor in the Bilirubin Rebound after Exchange Transfusion

E. KAUDER and A. M. MAUER. *Journal of Pediatrics* [J. Pediat.] 60, 163-171, Feb., 1962. 4 figs., 32 refs.

Repeated exchange transfusions are sometimes required in newly-born babies suffering from hyperbilirubinaemia owing to a secondary rise in the serum bilirubin level, and the part played by haemolysis in this bilirubin "rebound" has been investigated in three hospitals associated with the University of Cincinnati College of Medicine, Ohio.

The patients were suffering from rhesus incompatibility (14 infants), ABO incompatibility (6 infants), or hyperbilirubinaemia unassociated with incompatibility (20 infants). The blood haptoglobin levels were estimated by a modified peroxidase activation method at intervals up to 60 hours following 54 exchange transfusions; haptoglobin combines with haemoglobin liberated from erythrocytes to form a complex which is removed by the reticulo-endothelial system and thus the rate of disappearance of haptoglobin

globin from the circulation is an indication of the rate of erythrocyte haemolysis. The results strongly suggest that in many of these infants erythrocyte haemolysis contributed significantly to the bilirubin rebound. *R. M. Todd*

CLINICAL PAEDIATRICS

185. **Kanamycin by Mouth in the Treatment of *Escherichia coli* Gastroenteritis in Infants.** (La kanamycine "per os" dans le traitement des gastro-entérites à colibacilles du nourrisson)

J. MARIE, A. HENNEQUET, and C. ROUX. *Annales de pédiatrie* [Ann. Pédiat.] 38, 413-417, Feb. 2, 1962. 1 fig., 3 refs.

Of 71 babies admitted to the Hôpital des Enfants-Malades, Paris, suffering from various degrees of gastroenteritis due to infection with coliform bacilli 18 were treated by diet alone, with the usual supportive measures, and 53 with kanamycin sulphate by mouth in doses of 0.05 g. per kg. body weight for 7 days. The 18 babies treated by diet did not show the same good results as the 53 treated with the antibiotic. Examination of those treated with kanamycin revealed neither toxic side-effects nor any persistent increase in the blood concentration of the drug. It is concluded that if kanamycin does not eventually produce resistance in the causal organisms, as other antibiotics have done previously, it should prove a useful drug in the treatment of this common disorder. *Franz Heimann*

186. **Phenethicillin and Penicillin G in Acute Suppurative Otitis Media in Childhood**

R. A. McNEILL. *British Medical Journal* [Brit. med. J.] 1, 360-362, Feb. 10, 1962. 15 refs.

Phenethicillin is stated to produce good blood levels after oral administration and to be more active than benzylpenicillin against staphylococci but less active against pneumococci and streptococci. At the Royal Victoria Hospital, Belfast, of 48 patients aged 4 months to 12 years suffering from acute suppurative otitis media (62 ears in all) alternate cases were treated with either benzylpenicillin (given intramuscularly) or phenethicillin (given orally in a dosage of 125 mg. 6-hourly) for a minimum of 6 days during which time they stayed in hospital; in no case was myringotomy performed. Bacteriological studies in the 30 cases showing perforation and discharge from the ear revealed the causal organism to be *Staphylococcus aureus* in 21 (66%). The response to benzylpenicillin was a little more rapid than that to phenethicillin, but all the patients recovered quickly with a good middle ear and good hearing except for 2 who needed simple treatment some months later. Phenethicillin has the advantages that it is given orally and does not cause gastrointestinal upset. *T. A. Clarke*

187. **Five Cases of Lobar Tension Emphysema in Infancy; Importance of Bronchial Malformation and Value of Post-operative Steroid Therapy**

J. P. BINET, C. NEZELOF, and J. FREDET. *Diseases of the Chest* [Dis. Chest] 41, 126-133, Feb., 1962. 8 figs., 11 refs.

Giant or tension lobar emphysema presents in infants with severe respiratory distress and may necessitate urgent surgical treatment. In this paper from the Hôpital Laënnec, Paris, are described the cases of 5 infants with symptoms of

dyspnoea, cyanosis, rib retraction, and failure to thrive in whom there were the characteristic clinical and radiological features of this condition. All were treated by lobectomy of the affected lobe of the lung with one fatality. Examination of the specimens revealed abnormalities of the cartilaginous rings of the bronchi and bronchioles with bronchomalacia. In two of the specimens the pulmonary parenchyma was replaced by widespread cystic cavities lined by very abnormal epithelium and described as pulmonary cystic adenomatoid malformation. Postoperative collapse in 2 of the infants responded dramatically to intravenous hydrocortisone therapy. Presumably this complication was the result of pulmonary collapse-consolidation and the response to the steroid was due to reduction of bronchial oedema and to bronchodilatation. *Winston Turner*

188. **Primary Hypertonia of the Pulmonary Circulation in Children.** (Первичная гипертония малого круга кровообращения у детей)

I. K. ЕСТРОВА and S. I. LEVINA. *Вопросы Охраны Материнства и Детства* [Vop. Okhrany Materin. Dets.] 7, 44-49, Feb., 1962. 34 refs.

Of 3 patients who died from primary pulmonary hypertension who were investigated before and after death 2 were found to have persistent ductus arteriosus, which must have helped to relieve the pulmonary circulation, but no other cardiac lesion was found. All 3 had arterio-venous anastomoses of the glomus type, and 2 had elastosis of the branches of the pulmonary artery up to the level of the segmentary bronchi. These glomi were similar in structure to those found in the skin, and have not been described hitherto in lung tissues. The authors note that this form of primary pulmonary hypertension must be distinguished from the group of diseases in which the pulmonary hypertension is secondary.

Death occurred in one case immediately after closure of the patent ductus, in another during cardiac catheterization, and in the 3rd case from acute cardiac failure 2 days after operation. In all cases the radial arterial blood pressure was low; while in the only case in which it was possible to measure the pulmonary arterial pressure, this was found to be higher than that in the peripheral circulation. The anastomoses were most marked in a woman who died at the age of 24, having had symptoms for 14 years, and fewest (and less developed) in a girl aged 14 with a short history of relatively mild symptoms. It is suggested that these glomus-like structures have a complex action upon the circulation and perform both a haemodynamic and an intro-receptor function, as suggested by Schorn. *L. Firman-Edwards*

189. **Deaths in Congenital Adrenal Hyperplasia**

W. W. CLEVELAND, O. C. GREEN, and L. WILKINS. *Pediatrics* [Pediatrics] 29, 3-17, Jan., 1962. 1 fig., 10 refs.

The treatment of congenital adrenal hyperplasia previously described by Wilkins *et al.* (Bull. Johns Hopk. Hosp., 1950, 86, 249; Abstr. Wld Med., 1950, 8, 401) consists in continuous administration of cortisone or a related steroid in the minimal amount necessary to maintain suppression of urinary excretion of 17-ketosteroids and prevent progress of virilization, excessive growth, and epiphyseal development. Since 1950 at the Harriet Lane Home (Johns Hopkins Medical Center), Baltimore, 92 patients have been so treated, of whom 8 died—6 having the sodium-losing type of adrenal

hyperplasia and 2 the virilizing type. The cases are described, including the clinical features of the terminal illness. The cause of death in 3 of the patients with the sodium-losing type of disease was improper management—sudden withdrawal of steroids or administration of too much salt. In 4 patients death followed the onset of an illness, with fever, coma, and collapse accompanied also by signs of severe disturbance of the central nervous system. At necropsy on 2 of these patients the brain showed vascular congestion and some cellular degeneration. The remaining patient had hypertension and died from brain damage not directly related to the adrenal disease. The authors point out that the odd febrile illness remains unexplained. The salt-losing type is the most serious form of adrenal hyperplasia, and the 6 deaths that occurred in a total of 34 cases of this type represent a mortality which is considerably lower than that recorded before the introduction of cortisone therapy. Improvement in the management of cases should lead to further reduction in mortality. *M. C. G. Israëls*

190. Minimal Chronic Brain Syndromes in Children

R. S. PAINE. *Developmental Medicine and Child Neurology* [Develop. Med. Child Neurol.] 4, 21–27, Feb., 1962. 2 figs., 7 refs.

From the Children's Hospital Medical Center, Boston, comes this report on 40 children aged 4 to 12 years and one older patient aged 18, who were referred for private neurological consultation because of poor school work (22 cases), overactivity, nervousness, or emotional problems. Clumsiness was common. No previous diagnosis of neurological lesions had been made. In 31 cases definitely abnormal neurological signs were found, and of the electroencephalograms recorded in 17 cases 15 were abnormal or borderline. In 24 cases there was a history suggestive of "a plausible cerebral insult". The author suggests that his findings indicate subclinical impairment of cerebral function in each of four areas of the brain—motor, mental, sensory, and convulsive—confirming the postulation of the "syndrome of minimal brain damage". He lists the overt and borderline manifestations due to damage in each of the four areas.

Janet Q. Ballantine

191. Preliminary Clinical Trial of Carisoprodol in Infantile Cerebral Palsy

G. E. WOODS. *Developmental Medicine and Child Neurology* [Develop. Med. Child Neurol.] 4, 28–34, Feb., 1962. 13 refs.

Carisoprodol, a new drug chemically related to meprobamate, was given to 46 patients, including 5 adults, suffering from various forms of cerebral palsy. In most cases the dosage was 250 mg. twice daily; it was found that a minimum of 6 weeks' treatment was required before the result could be assessed. On the basis of reports from physiotherapists, speech therapists, school-teachers, and nurses, 33 of the patients showed improvement. Drowsiness was troublesome, but was found to respond to amphetamine. Irritability was also noted and the author suggests that thioridazine hydrochloride would prevent this. The best results were obtained in athetoid patients, while spastic diplegics, especially those who had been premature babies, also did well. This was admittedly not a controlled trial, but it indicates that further research into the value of carisoprodol in the treatment of cerebral palsy may be worthwhile.

Janet Q. Ballantine

192. Brain Abscess in Children

D. A. MCGREAL. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 261–268, Feb. 10, 1962. 5 refs.

The records of 30 children with brain abscess who were admitted to the Hospital for Sick Children, Toronto, in the 10-year period 1951–61 are reviewed, the object being to determine the features responsible for the high death rate (9 fatal cases). The aetiological factors in the brain infection were congenital heart disease in 8 cases, ear disease in 7, and various other infective lesions in 8; there was no apparent cause in 7. In the children with congenital cardiac lesions (4 male and 4 female, aged 4 to 13 years) convulsions and a focal neurological defect were frequent. The patients with ear disease were all over the age of 9 years and had a history of ear infection. The duration of symptoms was relatively short—2 to 3 weeks—and the common symptoms were headache, vomiting, anorexia, and fluctuating drowsiness. Of the 8 cases classified as due to various other causes, the abscess followed tonsillectomy in 3, general malaise and anorexia soon after the operation being the important features. The ages of the group of children in whom no cause for the brain infection was established ranged from 2½ months to 13 years. The electroencephalogram was abnormal in 23 out of 24 cases in which it was recorded. In 13 of these it was considered to be compatible with the presence of an abscess, in 5 the presence of an abscess was considered possible, and in 5 its presence was considered unlikely. Of the 18 cases in which the presence of the abscess was suspected the site was located accurately in 13 and incorrectly in 5.

Discussing the cause of the 9 deaths the author states that in 5 cases death was unavoidable but that in 4 (2 patients died after lumbar puncture) death could have been prevented. In the presence of a suggestive history the likelihood of an abscess should be continuously suspected, and for a "definitive diagnosis ventriculography or needle aspiration is necessary".

J. E. A. O'Connell

193. Recurrent Encephalomyelitis in Childhood

N. S. ALCOCK and H. L. HOFFMAN. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 40–44, Feb., 1962. 9 refs.

Encephalomyelitis is fortunately a relatively uncommon disease in children which, in the main, happens only once. But it can be a recurrent illness, as is well demonstrated in this paper from the Royal Devon and Exeter Hospital and the Royal United Hospitals, Bath, in which 6 children are reported, all of whom were victims of more than one attack. Although there is no particular similarity in the detailed clinical descriptions, there is sufficient in common to all 6 to justify them being grouped together. In the belief that the disease may be an antigen-antibody sensitivity reaction the incidents in the case histories which support this view are emphasized. Since infection may precipitate further attacks, careful supervision is necessary at the onset of any infection or if there has been contact with an infectious case. Corticosteroids would seem to have a firm place in the treatment of such cases should encephalitic symptoms develop.

David Morris

194. EEG and Epilepsy in Cerebral Palsy: [Review Article]

K.-A. MELIN. *Developmental Medicine and Child Neurology* [Develop. Med. Child Neurol.] 4, 180–183, April, 1962. 9 refs.

Public Health and Industrial Medicine

195. Are Periodic Health Examinations Worth-while?

L. WADE, J. THORPE, T. ELIAS, and G. BOCK. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 81-93, Jan., 1962. 2 figs., 5 refs.

In 1948 a programme was inaugurated of periodic medical examination of the headquarters staff of an oil company in New York, and in this paper an attempt is made to determine whether the objectives of this programme have been achieved. These objectives were: (1) to diagnose disease at its inception in order to prevent or reduce disability; (2) to defer total disability and death; (3) to educate employees concerning the importance of seeking advice whenever new symptoms appear; and (4) to inculcate healthy habits of hygiene, nutrition, and sleep. The authors state that the desirability of all these is beyond dispute.

The medical records of 765 males who had been under observation for a minimum period of 10 years were reviewed. Disability which persisted for 8 days or longer, excluding non-specific gastro-intestinal conditions or upper respiratory-tract infections, occurred in 241 of these employees. It was temporary, sometimes recurring, in 199, permanent in 8, and fatal in 34. Of the total of 280 disabilities only 104 were discovered during the periodic health examinations; 82 of the remainder, however, were also diagnosed at the dispensary when employees later sought advice. The remaining 94 disabilities were diagnosed by private doctors elsewhere. In 25 of the 34 employees who died the disease which eventually proved fatal was discovered at the dispensary during a periodic health examination; 3 others attended after developing symptoms, while in 6 the disease was diagnosed elsewhere.

A large number of non-disabling abnormalities were found as a result of periodic examination, the commonest being obesity; this was present in 292 out of 1,071 employees; but in spite of advice on diet only 10% achieved a satisfactory reduction in weight.

The authors conclude that although the original objectives were not conclusively achieved, doctors who are continuously available at places of employment can make a valuable contribution to health in industry. *Eirian Williams*

196. The Problem of Vaccination in Allergic Children. (Le problème des vaccinations chez les enfants allergiques)

R. MANDE, C. THÉRON, and N. DONAT. *Annales de pédiatrie* [Ann. Pédiat.] 38, 399-405, Feb. 2, 1962. 26 refs.

From their experience with 331 allergic children who received at the Hôpital des Enfants-Malades, Paris, various types of vaccination including that against smallpox, diphtheria, tetanus, whooping-cough, and poliomyelitis, as well as B.C.G. vaccination, the authors conclude that the former practice of depriving an allergic child of such vaccinations is not justified, provided a few precautionary measures are taken.

For vaccination against smallpox the authors use an attenuated formol vaccine. For that against diphtheria, tetanus, and whooping-cough they recommend dilution of the vaccine to 1:10 for the first injection followed by the

whole vaccine 8 days later. Of 88 allergic children who were vaccinated with B.C.G. none showed any evidence of aggravation of the allergic state. *Franz Helmann*

197. Effect of an Influenza Epidemic on a City Population

P. N. MEENAN and M. R. BOYD. *Lancet* [Lancet] 1, 96-98, Jan. 13, 1962. 8 refs.

This report from University College, Dublin, describes the epidemic of influenza A2 which occurred in the Republic of Ireland in January, 1961. It is suggested that the epidemic originated in the English Midlands, the disease having been brought to Ireland by the heavy volume of traffic over the preceding Christmas period. Virus typing appeared to confirm this.

Fifteen strains of influenza A2 virus were isolated, 4 out of 9 allantoically, allowing typing within 48 hours because of the initial high titre on first harvest. Tests of serum pools from blood transfusion donors (as representing the general population) showed the pre-epidemic antibody titre to be negligible. Tests for neutralizing antibodies and complement fixation and haemagglutination inhibition tests all showed a peak in February, with a falling off in May, 1961. Figures for the closure of schools during the period are presented to indicate the epidemic conditions [but unfortunately no details are given].

Mortality occurred particularly in the 65 to 75 age group as well as amongst patients over 75 who might have had some pre-epidemic antibody from previous contact with the strain of virus concerned. The authors conclude that the 1961 strain was more lethal than the strain of 1957.

Kurt Schwarz

INDUSTRIAL MEDICINE

198. Hazards to Health in Uranium Mining and Milling

V. E. ARCHER, H. J. MAGNUSON, D. A. HOLADAY, and P. A. LAWRENCE. *Journal of Occupational Medicine* [J. occup. Med.] 4, 55-60, Feb., 1962. 3 figs., 5 refs.

Large-scale mining and milling of uranium ores started in the United States during World War II. At first only a few workmen were employed, but since then there has been considerable expansion of the industry, particularly in the Colorado Plateau. In 1945 300 miners and 600 millmen were employed; in 1960 the corresponding figures were 5,760 and 3,000. This population was both white and non-white, the latter being largely Indian [presumably North and Central American Indians rather than Asians]. Throughout the world it has been recognized that such workmen are exposed to the hazards of ionizing radiations and the inhalation of mineral dust as a result of which, as exemplified by the miners at Schneeberg and Joachimsthal in Saxony and Bohemia, there is a high mortality from pneumoconiosis and cancer of the lung. Accordingly, at the request of the Health Officers concerned with the potential hazard, the U.S. Public Health Service, assisted by the Atomic Energy Commission and the local State Departments of Health, instituted in 1949 environmental studies in the uranium

mines and, in 1950, supplemented these by medical epidemiological studies. The present paper records the results of the medical studies made from 1950 to 1960. The analyses of results were mainly restricted to white workmen, the non-white population being too small for valid statistical treatment.

Each examination consisted of (1) occupational history; (2) social data for follow-up purposes; (3) physical examination; and (4) 10 to 15 different laboratory procedures [not specified], including 14 × 17-inch (36 × 43-cm.) chest radiographs. In 1957 and 1960 cytological examination of the sputum was added. Altogether 3,306 miners from about 400 mines were examined at least once between 1950 and 1957, but because of the high mobility of these miners, only about 800 had been examined more than once. All 3,306 have been followed up at least annually, and at April, 1959, contact had been lost with only 2% of the study group. The environmental findings are summarized. A working level of radon and radon products of 300 μm per litre, equivalent to 1.3×10^5 MeV. of potential alpha energy per litre, was recommended and accepted.

The medical findings and deaths were analysed, but at the time of reporting the analysis was incomplete. Several cases of silicosis were diagnosed and a sharp upward trend in suspicious findings on cytological examination of the sputum gave cause for grave concern. Among the mill workers a few cases of vanadium poisoning were observed and supported by detection of a trace of vanadium in the urine. The principal causes of death were investigated by a life-table technique whereby observed and expected deaths were compared. This part of the study was confined to white uranium miners and the findings are presented in histogram form. An increased prevalence of death from lung cancer among miners with 3 or more years' experience of underground working is interpreted as significant at the 95% confidence level.

Throughout the paper the authors emphasize that as yet the number of workmen is relatively small and the period over which they have been observed is not long. Moreover, many had previously been employed in mining elsewhere and relatively few had been exposed for as long as 3 years or more. The scheme has been in operation only since 1950.

[This project deserves the highest commendation. Its great merit is that it is a prospective study. The wisdom of the investigation is seen in the following quotations: "It was early realized that conclusive results would be obtained slowly, and that recommendations for environmental controls could not wait for medical findings which might portend a disastrous situation" and "a continuing program of education and promotion of improved environmental control is being accelerated".]

A. Melkielejohn

199. **Relation between Pulmonary Function and Radiological Type of Silicosis.** (Rapporti tra funzionalità polmonare a tipo radiologico della silicosi) E. SARTORELLI and P. SCOTTI. *Medicina del lavoro* [Med. d. Lavoro] 52, 569-577, Oct., 1961 [received April, 1962]. 8 figs., 8 refs.

At the Milan Clinic of Industrial Medicine the authors carried out a statistical study aimed at comparing the average values of pulmonary function tests in normal subjects and those in silicotic patients divided according to x-ray

type (Geneva classification) and according to occupation (miners and metal workers). The groups were as follows: (A) 520 normal adult males (297 miners and 223 metal workers); (B) 1,470 silicotic patients seen in the clinic between 1950 and 1960, consisting of 884 miners and 586 metal workers (persons engaged in the repair of refractory furnaces were excluded). Every occupational category was classified by x-ray appearances into 6 groups. The silicotic patients were also grouped by age and height. The standards of pulmonary function were the vital capacity (V.C.) and maximum expiratory volume in one second (M.E.V.S.) as these are the two used in Italy and in many other countries as valid tests of pulmonary function. The average V.C. and M.E.V.S. in each subgroup were calculated and also the average percentage difference from the corresponding normal values. Student's test was then used to determine: (1) whether there was any difference in pulmonary function between identical groups of miners and metal workers; and (2) whether any x-ray group of silicotics showed any significant difference in pulmonary function from any other x-ray group.

The results showed that: (1) there was no difference between the normal subjects in the 2 occupational groups of the same age and height; (2) there was a direct proportion between the normal spirometric indices and height and an inverse one for age; and (3) in no type of silicosis was there a significant difference between the average percentage differences from the normal in the 2 occupational categories, thus suggesting that neither occupation had any special influence on the average extent of disordered pulmonary function if the x-ray type were the same.

The final statistical evaluation showed that: (1) the average reduction in M.E.V.S. values was greater in all x-ray types of silicosis than that of the V.C. in all types; (2) the dispersal of M.E.V.S. values was less than that of the V.C. values in all types; (3) the average V.C. and M.E.V.S. values showed a significant statistical reduction for all types of silicosis compared with the normal; (4) with some exceptions, the average V.C. values in the various x-ray types of silicosis showed a significant difference; (5) the average M.E.V.S. values showed without exception a significant difference for all the various x-ray types. Thus in every x-ray type the M.E.V.S. showed an average degree of impairment of pulmonary function differing statistically from the average degree of impairment for all other x-ray types. This was not the case if the V.C. is used as the test. Hence the M.E.V.S. would appear to give more information in the appraisal of the degree of impairment of pulmonary function in silicosis.

W. K. Dunscombe

200. **The Size of Cotton Dust Particles Causing Byssinosis: an Environmental and Physiological Study** C. B. MCKERROW, S. A. ROACH, J. C. GILSON, and R. S. F. SCHILLING. *British Journal of Industrial Medicine* [Brit. J. Industr. Med.] 19, 1-8, Jan., 1962. 5 figs., 16 refs.

In this study of the size of cotton dust particles causing byssinosis 14 men between the ages of 28 and 54, including 2 of the authors of this paper and 12 cotton mill blow-room or card-room workers, were exposed in a plastic tent for periods of 3 to 4 hours to air-borne cotton mill dust either of unrestricted size distribution (total dust) or dust from which all particles of more than 7μ in diameter had been extracted (fine dust). In the first series of tests the tent was

set up in a room adjoining the settling chamber of the mill's "trash" removal system and connected to it by a pipe 6 inches (15 cm.) in diameter; the dust concentration inside the tent was therefore much greater than that in the card-room as a whole. In this test 8 workers, all of whom had worked for at least 11 years in the blowing or card-room and 4 of whom complained of symptoms of byssinosis, and 2 of the authors took part. The tests were carried out first on a Friday and the subjects were then divided into two groups; in one group the tests were repeated on the Monday morning and again on Tuesday and Wednesday morning and afternoon, while in the second group the tests were repeated only on Monday and Wednesday afternoons.

In the second series of tests (carried out about 8 weeks later) the tent was set up in the card-room between two carding engines so that the dust concentration would be similar to that normally encountered by card-room workers. The subjects were the same 6 cotton workers and the same 2 authors together with 4 additional cotton workers, all of whom had had at least 11 years' exposure to cotton dust; 6 of the cotton workers had symptoms of byssinosis. They were divided into two groups as in the first series and the same tests were carried out.

The tests showed a fall in the indirect maximum breathing capacity from 120 litres a minute to 110 litres a minute, the response to total dust being slightly larger than to fine dust, but the concentration of fine particles in the unfiltered air was slightly higher. The changes in the single-breath nitrogen clearance index and in the inspiratory airways resistance were less constant, but the general pattern followed that of the indirect maximum breathing capacity. The authors conclude that the fine fraction of cotton mill dust (less than 7μ in diameter) produces changes in respiratory function and may be alone responsible for byssinosis. They consider that the findings suggest a direct action by the dust on the smaller air passages and therefore imply that to be completely effective dust suppression measures in cotton mills should be such that all fine dust is removed. *Kenneth M. A. Perry*

201. The Attack Rate of Progressive Massive Fibrosis.

A. L. COCHRANE. *British Journal of Industrial Medicine* [Brit. J. Industr. Med.] 19, 52-64, Jan., 1962. 5 figs., 22 refs.

The author reports an 8-year follow-up study of miners and ex-miners in two Welsh valleys, with a view to discovering factors related to the attack rate of progressive massive fibrosis (P.M.F.). The population study and method of comparing radiographs are described; it is suggested that the "average category" (that is, of the first and follow-up radiographs) might best be related to the number of cases of P.M.F. found on comparison of the two films. The attack rate of P.M.F. is probably the main measure by which the safety of "proved" dust conditions will be judged. In contrast to the effect of age on progression of P.M.F., there was no significant relation between the subject's age and attack rate.

In one of the two valleys exogenous tuberculous infectivity had been vigorously controlled but, it is suggested, without increase in the decline of infectivity compared with the other valley. There was a fall in tuberculous infectivity in both valleys over the period, but without evidence of related decline in the attack rate of P.M.F. No conclusive evidence of any effect of antecedent (healed) tuberculous infection on

the attack rate was found. The "heaviness" or otherwise of work performed during the period between the surveys did not seem to have affected the attack rate, nor was the latter significantly affected either by body-type or smoking habits.

Curves relating the attack rate to the average category of pneumoconiosis showed a very marked rise in attack rate with each higher category of pneumoconiosis, the lesson to be learnt from this being that the aim should be to prevent the progression of pneumoconiosis past Category I. In discussing the aetiology of P.M.F. the author suggests that it is doubtful whether P.M.F. is related to the amount (or even the presence) of silica in the lungs, and the effect of associated non-specific infections in causing P.M.F. is thought to be unimportant; but the evidence that coal dust plus tuberculous infection causes P.M.F. is strong, though the present (epidemiological) study may not actually support it. He concludes that the evidence of increased progression of simple pneumoconiosis during the past 8 years among coal-face workers in this area suggests that either the present level of the agreed "approved" conditions is too low or that in some pits the "approved" conditions were not in fact achieved. *L. W. Hale*

202. Ventilatory Capacity in Miners: a Five-year Follow-up Study

I. T. T. HIGGINS and P. D. OLDHAM. *British Journal of Industrial Medicine* [Brit. J. Industr. Med.] 19, 65-76, Jan., 1962. 2 figs., 20 refs.

In 1954 the ventilatory capacity was determined in a representative sample of men living in the Rhondda Fach valley, with particular regard to the effect upon it of age, type of occupation, exposure to coal dust, and category of simple pneumoconiosis (Carpenter *et al.*, *Brit. J. Industr. Med.*, 1956, 13, 166; *Abstr. Wild Med.*, 1957, 21, 141). The authors now report a 5-year follow-up study which was made because changes found at second examination might be expected to be more closely related to environment than the absolute level found at any single time. In this study interim occupations between the surveys, respiratory symptoms and illnesses, and smoking habits were recorded. The forced expiratory volume, expressed as the indirect maximum breathing capacity (I.M.B.C.) was measured, height and weight recorded, and a postero-anterior chest radiograph taken. The comparability of the two groups was considered satisfactory. Of special interest were the changes found at second examination compared with those predicted from the trend for age in a cross-sectional survey; the method of presenting results is explained. Possible explanations of the findings as to the relation of I.M.B.C. to age, mining, and smoking habits are considered.

The change in I.M.B.C. over the 5-year interval seemed to be independent of age. The average decline in I.M.B.C. was not increased by mining or by dust exposure measured in years. Men having respiratory symptoms at follow-up examination were found to have an increased decline in I.M.B.C. Smoking, especially heavy smoking, reduced the I.M.B.C. among the non-miner group. Among miners without pneumoconiosis there was a greater reduction in I.M.B.C. in smokers than in non-smokers (but without relation between the reduction and the amount smoked). Men with Category 3 pneumoconiosis showed no correlation between reduction of I.M.B.C. and smoking habits. The

results support previous findings on the importance of effect of age, smoking, and respiratory symptoms on ventilatory capacity, but do not throw much light on the reason why miners' values are lower than those of non-miners (after standardizing for smoking the difference remained): the difference is apparent at an early age after entering the industry and seems to cease to be operative at the age-span studied in this group. The limitations of "longitudinal" (follow-up) studies are pointed out.

L. W. Hale

203. Clinical Manifestations following Exposure to Centimetre Range Waves for Long Periods. (Некоторые клинические проявления хронического воздействия сантиметровых волн)

E. A. DROGIČINA, M. N. SADČIKOVA, D. A. GINZBURG, and N. A. ČULINA. *Гигиена Труда и Профессиональные Заболевания* [Gig. Tr. prof. Zabol.] 6, 28-34, Jan., 1962. 3 figs., 16 refs.

Chronic exposure to centimetre-range waves in industrial conditions is known to cause various manifestations of disturbance of the autonomic nervous system. In order to study these changes, the authors have investigated the cutaneous-galvanic reflex and the electroencephalogram (EEG) in subjects showing clinical features resulting from such exposure, both at rest and in the course of application of light and sound stimuli. Other tests included estimation of thyroid function (uptake of ^{131}I) and morphological and biochemical examinations of the blood.

These tests revealed that there was increased excitability of the central divisions of the autonomic nervous system. The EEG showed the presence of slow theta and delta waves, sporadic in character, in 50% of the subjects, and thyroid function was increased, with clinical signs of thyrotoxicosis in one or 2 cases. These changes were reversible in persons exposed to the action of centimetre waves for shorter periods, but with longer periods of exposure the effect was more marked, and permanent or progressive. In such patients vascular changes (angiospastic crises) were the most prominent features, giving rise in some cases to cardiac pain or to transient unconsciousness, together with changes in the fundus oculi. From all the available evidence it is concluded that chronic exposure to centimetre-range waves may lead to pathological changes in the diencephalon.

Basil Haigh

204. The Comparative Toxicity of Dusts of Metallic Alloys. (Исследования по сравнительной гигиенической оценке пыли металлических сплавов)

O. JA. MOGILEVSKAJA. *Гигиена Труда и Профессиональные Заболевания* [Gig. Tr. prof. Zabol.] 6, 8-14, Jan., 1962. 3 figs., 9 refs.

The object of this investigation was to study the relationship between the toxicity of dust of metallic alloys and the toxicity of the individual component metals. Alloys of iron and nickel (Fe-Ni) containing 30% of Ni; of iron and molybdenum (Fe-Mo) containing 10% of Mo; and of iron, aluminium, and beryllium (Fe-Al-Be) containing 13% of Al and 3% of Be were pulverized so that 80% of the particles were less than 2μ in diameter, and 50 mg. of the dust, emulsified in 0.5 ml. of sterile physiological saline, was injected intratracheally into 30 white rats, a further 5 rats serving as controls. The animals were killed 8 months later and the lungs examined histologically.

The toxicity of the metals in alloy form differed from that of identical doses of the pure metals, probably because of their physical and physico-chemical properties. The Fe-Ni alloy dust was much less toxic than an equivalent dose of pure nickel dust of the same degree of dispersion, and the same phenomenon was observed, although to a lesser degree, in the case of the Fe-Mo alloy. The toxicity of the beryllium incorporated in the triple alloy was less marked than that of an equivalent dose of beryllium oxide. The toxic action of this triple alloy differed from that of aluminium and of iron alone. It is concluded that the toxic effect of the dust of a metallic alloy is not equivalent to the sum of the toxic effects of the dusts of the constituent metals.

Basil Haigh

205. Porphobilinogen and Uroporphyrin in the Urine in Lead Poisoning. (Porfobilinogeno e uroporfirine nelle urine dei saturnini)

L. MOREO. *Medicina del lavoro* [Med. d. Lavoro] 52, 561-568, Oct., 1961 [received April, 1962]. 3 figs., 28 refs.

At the Clinic of Industrial Medicine, Milan, the author used a spectrophotometric method to carry out investigations on coproporphyrin (CP), uroporphyrin (UP), and porphobilinogen (PBG) levels in the urine in the following groups of patients: (A) 9 with lead colic; (B) 14 with chronic lead poisoning without colic; and (C) 6 with signs of increased lead absorption.

The results (in mg. per 24 hours) were as follows. In Group A, CP 0.39 to 0.88 (there was one exceptional result of 3.68); UP 0.1 to 0.39; PBG 0.4 to 1.7. In Group B, CP 0.09 to 0.42 (in 1 case 1.04); UP absent in 10 and in the remainder ranged from 0.13 to 0.88; PBG 0.3 to 1.5. In Group C, CP 0.13 to 0.30; UP absent in all; PBG 0.5 to 1.1.

In Group A urinary excretion of UP was raised in all cases, but that of PBG was within normal limits. Two patients in this group were treated with sodium calciumedetate (2 g. intravenously); here the excretion of CP fell rapidly and that of UP also, these substances disappearing from the urine on the 8th and 11th days respectively. [No comments are offered on the single patient with the exceptional excretion of CP, on the 4 patients in Group B in whom UP was present in the urine, or on Group C.]

The author considers that there was no evident quantitative relationship between the elimination of CP and of UP in the various patients, but there was a definite relationship between the presence of UP in the urine and the degree of lead poisoning, as the former was always accompanied by definite clinical signs and symptoms such as the blue line and punctate basophilia. There was no relation between the occurrence and degree of UP excretion and the intensity of the anaemia. He considers that the discovery of UP in the urine of patients with chronic lead poisoning with a raised excretion of CP and nearly normal urinary PBG content confirms the existence of an enzyme blockage in the more advanced phases of porphyrin maturation (coproporphyrin into protoporphyrin), and its diminution after treatment with sodium calciumedetate can be explained by a reduction in enzyme blockage through chelation of the circulating lead.

W. K. Dunscombe

206. Industrial Dermatoses

A. JOHNSON. *New Zealand Medical Journal* [N.Z. med. J.] 61, 38-49, Jan. [received March], 1962. 10 refs.

Toxicology

207. Salicylates and Gastro-Intestinal Bleeding: Acetylsalicylic Acid and Aspirin Derivatives

P. H. N. WOOD, E. A. HARVEY-SMITH, and A. ST. J. DIXON. *British Medical Journal* [Brit. med. J.] 1, 669-675, March 10, 1962. 6 figs., 26 refs.

A study of gastro-intestinal haemorrhage associated with administration of salicylates is reported from Hammersmith Hospital and the Postgraduate Medical School, London. Faecal blood loss was determined in 144 patients who received 15 g. of aspirin 4 times daily or an equivalent dosage of an aspirin preparation, the patient's erythrocytes being labelled with radioactive chromium. Of the 144 patients 93 had rheumatoid arthritis, 41 suffered from various disorders, including 24 with a history of peptic ulceration, and 10 were healthy volunteers. All the preparations caused bleeding of about the same degree with the exception of effervescent aspirin ("alka-seltzer"), a highly alkaline product, and a new preparation, aloxiprin ("palaprin"), an insoluble neutral compound of aluminium aspirin in polymeric form, which caused significantly less bleeding than aspirin in about one-third of the patients receiving these two drugs.

V. J. Woolley

208. Aspirin Preparations and Their Noxious Effect on the Gastro-Intestinal Tract

L.-TH. F. L. STUBBÉ, J. H. PIETERSEN, and C. VAN HEULEN. *British Medical Journal* [Brit. med. J.] 1, 675-680, March 10, 1962. 4 figs., 28 refs.

In an investigation at University Hospital, Leiden, the Netherlands, the presence of blood in the faeces was demonstrated by the benzidine test in 61% of 421 patients who received 1.5 to 3 g. daily of aspirin or one of its soluble salts. Preparations of aspirin which caused the least blood loss were "alka-seltzer" tablets in solution and tablets coated with calcium acetatephthalate; with the latter preparation there was a high serum aspirin level without gastric irritation. Sodium salicylate and salicylamide did not cause bleeding but were inadequate as analgesics.

V. J. Woolley

209. The Use of Phenacetin by and Its Detrimental Effects on a Series of Hospital Patients. [In English]

A. KISANEN and H. A. SALMI. *Annales medicinae internae Fenniae* [Ann. Med. intern. Fenn.] 50, 195-204, 1961. 10 refs.

To determine the extent to which phenacetin is consumed in Finland a questionnaire was sent to 800 patients treated at the Medical Clinic of the Central Hospital, University of Turku. Analysis of the replies showed that 20% of the patients took analgesics daily and 30% weekly and that women took analgesics more frequently than men. The favourite preparations were powders containing phenacetin. The habit was most common in women aged 41 to 50 years and in men aged 51 to 60. Social status, occupation, or a town or country environment did not influence the habit. Anaemia (Hb < 11 g. per 100 ml.) was present in 12% of those who took no analgesics and in 25% of habitual consumers of phenacetin. Of the patients with renal disease, 35% took analgesics daily compared with 17% of those without this disease. The authors state that the incidence

of renal disease was directly proportional to the total quantity of phenacetin consumed [but no evidence is presented that phenacetin caused the renal disease. Nevertheless, it does appear that the regular consumption of analgesic powders is an unnecessary habit in many people.]

T. B. Begg

210. Estimation of Arsenic in Biological Tissue by Activation Analysis

H. SMITH. *Journal of Forensic Medicine* [J. forens. Med.] 8, 165-171, Oct.-Dec., 1961. 3 figs., 3 refs.

In this paper from the University and the Western Regional Hospital Board, Glasgow, non-destructive methods are described for the quantitative and qualitative determination of arsenic present in human hairs, artificially induced radioactivity being measured in a variety of ways.

It is pointed out that the stable trace elements present in the hair are activated by placing it in a flux of thermal neutrons and the consequent radioactive emissions are measured in sections, a Geiger counter being used. In normal hair, the activity is largely due to sodium distributed fairly uniformly along the organic matrix of the shaft. Traces of arsenic, however, will raise the count, causing a peak of activity, and from the position of this peak relative to the bulb, the approximate rate of growth being known, the time of ingestion of the arsenic may be calculated with reasonable accuracy. It is shown that in order to produce a recognizable peak the concentration of arsenic should be about 30 p.p.m.

An autoradiographic method in which the activated hair is allowed to "photograph" its activity on to photographic emulsion is also mentioned, but this is considered to be generally less sensitive than the method described above, requiring concentrations of the order of 50 p.p.m. Two quantitative methods are briefly described, which depend on transmission values through aluminium and calculations based on the half-life of arsenic and sodium respectively; an accuracy of the order of 85 to 95% is claimed from a series of 12 estimations.

The disadvantages of these techniques are their relative insensitivity to low concentrations of arsenic and the fact that conventional analysis is almost always required as well to establish that the radioactivity measured is, in fact, due to arsenic.

Gilbert Forbes

211. The Use of Succinic Acid in the Treatment of Acute Carbon Monoxide Poisoning. [In English]

S. GERSHON, E. R. TRETHEWIE, and M. CRAWFORD. *Archives internationales de pharmacodynamie et de thérapie* [Arch. int. Pharmacodyn.] 134, 16-27, Nov. 1, 1961. 2 figs., 18 refs.

At the Medical Faculty of the University of Melbourne succinic acid was tested for its resuscitative effect on animals rendered comatose by acute carbon monoxide poisoning. A total of 63 healthy white guinea-pigs weighing from 200 to 450 g. were exposed, usually in pairs, to a slow current of washed coal-gas for 2 minutes in a glass tank of 4.5 litres capacity, the tank being full of air initially. The gas inflow was adjusted to maintain a slight positive gas pressure of 150 to 170 ml. per minute in the tank. On removal from

the tank the animals were comatose and completely flaccid, respiration was usually very shallow, and no corneal or withdrawal reflexes could be elicited. One animal of each pair was injected intraperitoneally with 1 to 2 ml. of 10% succinic acid solution and the times taken for the corneal reflex to return and the animal to make its first successful attempt to right its head were noted. The mean time of collapse was 1.5 minutes and anoxic convulsions occurred in 60 animals. The corneal reflex in 17 control animals took an average of 2 minutes to return, and in 9 animals which received succinic acid took 1.2 minutes. In the remainder (22 test and 13 controls) the reflex returned at once. The control animals took an average of 4 minutes for the righting reflex to return compared with 2.5 minutes in the test animals.

Similar experiments were carried out on dogs, cats, and rabbits. Nine cats were used. On removal from the tank the animals were comatose, usually rigidly extended and with very fast, shallow respiration gradually returning to normal over 8 to 12 minutes. Five of the cats were injected intraperitoneally with 2 to 5 ml. of succinic acid on removal. There was immediate improvement in respiration and the corneal reflex returned within 1 minute followed by righting movements in 5 to 6 minutes. In one cat the injection of succinic acid caused extreme convulsive spasms terminating fatally; a large amount of fluid exudate and a certain amount of blood was found post mortem in the lungs. Five minutes' exposure to coal gas was fatal to just over 50% of rabbits left untreated after removal. Three animals exposed for this time were comatose on removal, but showed a dramatic return to consciousness and normal activity after 0.8 to 1.0 ml. of 10% succinic acid had been injected intravenously. Three mongrel dogs were rendered comatose by exposure to coal gas, but 1 to 2 minutes after being injected intravenously with 15 ml. of 10% succinic acid were able to walk.

One human patient, comatose for 16 hours owing to coal-gas poisoning, was injected with a total of 20 ml. of 10% succinic acid. The injection produced a marked respiratory stimulation and rise in blood pressure, but no alteration in the level of consciousness was noted till 12 hours later, when the patient regained consciousness.

Electrocardiographic studies showed that as gassing proceeds the T wave and R wave fall slightly in potential, and with the onset of apnoea the T-wave potential increases greatly. These changes are restored to normal by succinic acid.

Freshly drawn sheep's blood was diluted 1 in 100 with mammalian tyrode solution. This solution was investigated spectrophotometrically for aerated blood and blood through which coal gas was bubbled for 20 seconds. A similar set of experiments was carried out on blood containing 0.25% buffered succinic acid (pH 7.2). A measurable change in the absorption spectrum occurred within 1 minute of adding succinic acid to the solution at the 2 maxima for carboxyhaemoglobin, these alterations being opposite in sign to those produced during the transformation from haemoglobin to haematin promoted by 0.25% succinic acid. Nicotine tartrate and acetic acid were used to evaluate various factors in recovery. Nicotine stimulated respiration but had undesirable side-effects. Buffered acetic acid produced no change in the recovery rate.

The possible actions of succinic acid to be considered are: respiratory stimulation, which increases the removal of carbon monoxide from the body; an increase of oxyhaemoglobin over carboxyhaemoglobin formation in the presence

of carbon monoxide as well as oxygen in the alveolar air; and direct stimulation of cellular metabolism, particularly in the central nervous system and functional tissues of the heart.

Anne Tothill

212. Carbon-monoxide Poisoning: a Comparison between the Efficiencies of Oxygen at One Atmosphere Pressure, of Oxygen at Two Atmospheres Pressure, and of 5% and 7% Carbon Dioxide in Oxygen

T. A. DOUGLAS, D. D. LAWSON, I. MCA. LEDINGHAM, J. N. NORMAN, G. R. SHARP, and G. SMITH. *Lancet* [*Lancet*] 1, 68-69, Jan. 13, 1962. 3 refs.

This paper from the Western Infirmary and the Veterinary Hospital, Glasgow, reports a study of resuscitation from carbon monoxide poisoning in animals. The results were compared of 4 methods of treatment, namely, with (1) oxygen at one atmosphere pressure, (2) oxygen at 2 atmospheres pressure, (3) 5% carbon dioxide in oxygen (5% carbogen), and (4) 7% carbon dioxide in oxygen (7% carbogen).

Twenty dogs were used and each was exposed to carbon monoxide until the blood level of carboxyhaemoglobin (COHb) reached 70%. To 10 of the dogs (Group A) the gas was given as a mixture of carbon monoxide in oxygen for 45 minutes; the other 10 dogs (Group B) were slowly intoxicated over a period of about 2 hours with a mixture of coal gas and air containing 0.37% carbon monoxide. In each experiment the dog was revived by the use of one of the four methods of treatment listed above and the time was noted when the blood COHb level was reduced to 35%—the "half-clearance time". The experiment was carried out 4 times on each dog, a different treatment being used on each occasion and a few weeks' interval being allowed after each test. In Group A a Heidbrink valve and rebreathing bag were placed in circuit, while in Group B a Rüben non-return valve was fitted.

The mean half-clearance times in minutes for each group are given below. For treatment with oxygen at one atmosphere pressure the figures are for 4 dogs only, whereas for the other methods of treatment the figures are those for all 20 dogs.

	Oxygen at 1 atmos- phere	Oxygen at 2 atmos- pheres	Carbogen 5%	Carbogen 7%
Group A Mean S.D.	29.8 ±4.8	8.6 ±1.9	20.6 ±4.9	16.3 ±4.6
Group B Mean S.D.	— —	7.6 ±2.7	13.8 ±3.9	13.4 ±3.7

All the dogs recovered without detectable injury. The superlative effect of oxygen under pressure is thus established. Inhalation of oxygen under pressure swiftly expels the carbon monoxide from the erythrocytes of the blood, while the tissue anoxia is directly relieved by the considerable volume of oxygen dissolved in the plasma.

[This is a very important paper making a valuable contribution to the study of resuscitation from carbon monoxide poisoning.]
M. A. Dobbin Crawford

Anaesthetics

213. Electroencephalographic Effect of Hypercarbia during Nitrous Oxide-Oxygen-Thiamylal-Demerol Anesthesia

V. L. BRECHNER, R. O. BAUER, G. E. BENSTON, R. M. BETHUNE, G. MAISEL, and J. B. DILLON. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 91-104, Jan.-Feb., 1962. 2 figs., 10 refs.

The major EEG [electroencephalographic] alteration resulting from hypercarbia during nitrous oxide-oxygen-thiamylal-"demerol" anesthesia is a gradual but progressive reduction in voltage. This depression of amplitude may be expected to be noticeable at alveolar CO₂ percentages of 7.5 to 8. Slow wave forms (1 to 4 cps [cycles per second]) appear less frequently than voltage depression. Cardiovascular and ECG [electrocardiographic] alterations are poorly correlated with the degrees of hypercarbia employed in this study (10% or less). An increase in tidal and minute volume occurs in the spontaneously respiring patient at the same degree of hypercarbia as that which usually causes minimal reduction in amplitude of EEG wave forms.—[Authors' summary.]

214. Effects of Dry Anaesthetic Gases on the Respiratory Mucous Membrane

J. D. K. BURTON. *Lancet* [Lancet] 1, 235-238, Feb. 3, 1962. 4 figs., 5 refs.

The author has studied the movement of mucus in the trachea of dogs anesthetized for heart-lung bypass operations at St. Thomas's Hospital, London. Traces of indian ink were applied through a bronchoscope to mark the mucus at carinal level. Under pentobarbitone anaesthesia with the animals breathing air through the nose the ink marks were found to pass up the trachea and through the vocal cords in 20 to 30 minutes. The rate of movement was depressed by atropine premedication, but the effect wore off after a few hours. A cuffed endotracheal tube blocked the passage of mucus at the level of the inflated cuff. Dry anaesthetic gases administered for 3 to 5 hours caused a marked reduction in the rate of movement of mucus. Under similar conditions but with humidified anaesthetic gases the movement of mucus was normal.

The significance and clinical application of this finding are discussed and 2 illustrative cases in human beings described. A plea is made for humidification of anaesthetic gases if anaesthesia is expected to last some hours.

J. V. I. Young

215. Alterations in Response to Somatic Pain Associated with Anaesthesia. IX: The Effects of Hypercarbia and Catecholamines

J. W. DUNDEE, G. W. BLACK, and R. M. NICHOLL. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 24-30, Jan., 1962. 4 figs., 28 refs.

With the aid of a method of analgesimetry based upon the measurement of the pressure, which when applied to the subcutaneous surface of the tibia would produce pain, it was shown in man that the inhalation of carbon dioxide produced marked and consistent analgesia. This was noted

both when this gas was inhaled directly in concentrations of 5 to 10% and when endogenous carbon dioxide was allowed to accumulate during 10 minutes rebreathing in a closed circuit. It was not possible to demonstrate a quantitative relationship between the degree of hypercarbia, as assessed by the end-tidal Pco₂, and the increase in the analgesimetry readings.

It seemed that the analgesic effect might be mediated through the release of catechol amines which is associated with hypercarbia. This was to some extent confirmed when it was demonstrated that 5 µg. per minute of adrenaline infused intravenously into volunteers over 4 minutes produced a rise in analgesimetry readings. Noradrenaline in similar quantities, however, had no such effect.—[Authors' summary.]

216. Effect of Micoren, Ethamivan and Nikethamide on Thiopental Recovery

A. B. DOBKIN, A. McL. KEIL, and P. C. ALBANO. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 58-68, Jan.-Feb., 1962. 2 figs., 33 refs.

The authors, working at the Upstate Medical Center, Syracuse, New York, suggest that analeptic drugs can advantageously be tested on patients immediately after anaesthesia.

After defining their criteria of effectiveness of analeptic drugs they then describe an investigation carried out on women undergoing elective dilatation and curettage under thiopentone and nitrous-oxide-oxygen anaesthesia. At the termination of surgery each patient received 150 mg. of "micoren", 75 mg. of vanillic acid-diethylamide (ethamivan), 375 mg. of nikethamide ("coramine"), or no analeptic agent. Recovery time was recorded in minutes from the moment of removal of the face mask until certain specific end-points (described) were reached. It was found that none of the analeptic drugs tested shortened the duration of sleep after thiopentone. There were no striking changes in pulse or blood pressure with any of the drugs and none of them caused irritation at the site of injection. All three agents produced a marked increase in respiratory depth, often accompanied by coughing or sneezing. The results of the investigation are discussed at length.

Mark Swerdlow

217. The Action of Thiopentone on the Vascular Distensibility of the Hand

W. E. WATSON, E. SEELYE, and A. C. SMITH. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 19-23, Jan., 1962. 2 figs., 25 refs.

The distensibility of the capacity blood vessels of the hand was investigated in 7 patients who received an induction dose of thiopentone before an elective minor surgical procedure and in one patient receiving intermittent positive pressure respiration. Thiopentone caused a transient decrease of diastolic arterial blood pressure and of pulse pressure in 6 of the 7 patients and in the totally paralysed patient. This was associated with a transient increase in distensibility of

the capacity blood vessels of the hand. Thiopentone caused a decrease in the distensibility of the capacity blood vessels in one subject; this subject suffered no fall in arterial blood pressure.—[Authors' summary.]

218. Oral Premedication in Children: a Controlled Clinical Trial of Pecazine, Trimeprazine and Methylpentynol

A. G. DOUGHTY. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 80-89, Feb., 1962. 13 refs.

The only discernible effect of pecazine-hyoscine was slightly to decrease salivary secretion. Apart from decreased palatability, no other significant differences were observed between it and the control, hyoscine-only. The absence of any obvious pharmacological effect could be due to underdosage and incorrect timing of administration.

Trimeprazine-hyoscine was associated with unsatisfactory behaviour in the anaesthetic room as compared with the control, but this disadvantage was offset by potent anti-salivary and anti-emetic effects and a satisfactory memory of the induction of anaesthesia. It also appears to be reasonably palatable in solution, but against this advantage must be noted a marked association with postoperative pallor.

Methylpentynol-hyoscine was an unpalatable preparation; nevertheless a high proportion of children behaved well in the anaesthetic room but not significantly better than those who had received the control solution. There was a slight but inadequate suppression of salivary secretion and an unexpectedly marked anti-emetic effect.

Considering that the control solution [hyoscine] contained no recommended sedative it was remarkable for the good behaviour of the children in the anaesthetic room. On the other hand, the antisalivary effect was inadequate and there was a fairly high incidence of postoperative vomiting.—[From the author's summary.]

219. Inadvertent Hypothermia in Paediatric Surgery and a Method for its Prevention

D. G. CALVERT. *Anaesthesia* [Anaesthesia] 17, 29-45, Jan., 1962. 8 figs., 16 refs.

The temperature changes of 180 children undergoing surgery [at the Westminster Children's Hospital, London] are presented and examined. Anomalies between the temperature changes of hydrocephalic children undergoing neurosurgical procedures and children undergoing non-neurosurgical procedures have been found. A method of preserving the temperature stability of young children undergoing surgery is described. The causes of a drop in body temperature in children are reviewed. The effects of inadvertent hypothermia on various aspects of post-operative progress are presented. The beneficial effects of preventing inadvertent hypothermia during operation on young children are presented.—[Author's summary.]

220. A Double-blind Study of Tacaryl as a Narcotic Potentiator when Used for Preliminary Medication

W. H. L. DORNETTE, M. F. POE, R. J. CAVALLARO, and W. E. SHEFFIELD. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 32-36, Jan.-Feb., 1962.

Methdilazine hydrochloride ("tacaryl") was given for premedication to 195 adult patients undergoing elective surgery at the City of Memphis Hospitals, Tennessee. Each patient

received, under double-blind conditions, one of the following: (1) 100 mg. pethidine with 0.5 ml. of a placebo; (2) 12.5 mg. of tacaryl; (3) 12.5 mg. of tacaryl with 50 mg. of pethidine; or (4) 0.5 ml. of a placebo. The medication was given intramuscularly together with 0.4 mg. of atropine one hour before anaesthesia. During the preoperative examination the blood pressure and respiration rate and volume were recorded, these measurements being repeated immediately before induction of anaesthesia when the degree of sedation achieved was assessed.

It was found that none of the 4 medications caused over-depression. Only a few of the patients who received active drugs were apprehensive, whereas more than half the patients given a placebo were considered to be "very apprehensive". The majority of the patients in all 4 groups showed a change of less than 20 mm. Hg in systolic pressure above or below the premedication level. The respiratory minute volume was depressed in 70% of patients receiving pethidine with tacaryl, 59% of those given pethidine with a placebo, and 55% of those given tacaryl alone.

The authors consider that the combination of tacaryl and pethidine has no clear-cut advantages over pethidine alone.

Mark Swerdlow

221. The Effects of Anesthesia on Liver Function during Labor

B. SMITH, F. MOYA, and S. SHNIDER. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 24-31, Jan.-Feb., 1962. 6 figs., 18 refs.

Eighty per cent of a group of 98 healthy pregnant patients who underwent bromsulphalein dye excretion tests during labor and prior to anesthesia had more than 5% dye retained after 45 minutes. The average dye retention for this group was 9.13%. There was no association found between duration of labor at the time of injection and amount of dye retained.

In 76 patients the bromsulphalein test was repeated during the postpartum period in order to study the effects of anesthesia on the liver. The average dye retention decreased during the postpartum period and usually reached normal levels on the fourth day regardless of the anesthetic technique. No significant differences were noted between chloroform analgesia, cyclopropane, regional, or local anesthesia.

It was concluded that the liver of pregnancy was not any more susceptible to anesthesia than in the nonpregnant state, and that factors other than anesthesia were of greater importance in determining the ability to excrete bromsulphalein following delivery.—[Authors' summary.]

222. Variation in Performance of Boyle Vaporizers Calibrated for Halothane

A. R. DE C. DEACOCK. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 39-43, Jan., 1962. 3 figs., 4 refs.

Six Boyle bottles calibrated for halothane vaporization were re-examined after a period of use. Two units delivered substantially less and one delivered substantially more than the indicated concentration of vapour. Changes in performance were found to be due to the accumulation of grease in the various openings in the control taps of the vaporizers. The use of the Boyle bottle for the administration of halothane is discussed and certain recommendations are made.—[Author's summary.]

Radiology

RADIODIAGNOSIS

223. The Posterior Inferior Cerebellar Artery on Vertebral Angiography

B. S. WOLF, C. M. NEWMAN, and M. T. KHLNANI. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 322-337, Feb., 1962. 19 figs., 9 refs.

Vertebral angiography has been principally used in the diagnosis of aneurysm, arterio-venous malformations, and tumours with pathological vasculature in the posterior fossa. The diagnosis of space-occupying lesions in the absence of any kind of contrast filling purely on the basis of displacement of vessels has never received the attention that has been given to the diagnosis of similar supratentorial lesions by carotid angiography. The main reason for this is the wide variation in the origin and course of the branches of the vertebral artery. In the study here reported from the Mount Sinai Hospital, New York, an attempt was made to discover a typical pattern for the posterior inferior cerebellar artery since this would make the recognition of normal and pathological variations easier.

The typical configuration of this artery in both the lateral and half-axial antero-posterior projections is first described and some of the normal variations are discussed. Thereafter the various pathological distortions and displacements of the artery are described and their significance in the recognition and location of space-occupying lesions is discussed. Particular attention is paid to the apical portion of the cranial loop, it being pointed out that the apex of the cranial loop seldom lies more than one millimetre below a line drawn parallel to Twining's line, but passing through the lower margin of the internal auditory meatus. This relationship may therefore be used as an approximate guide in a supero-inferior direction to the normal position of the apex of this loop. In addition, a method of semi-quantitative estimation of antero-posterior displacement of the apex of this loop in the lateral projection is outlined. The method is based on measurement of the distance between the foot of a line drawn perpendicular to Twining's line and the tuberculum sellae, this distance being expressed as a percentage of the complete length of Twining's line, that is, the distance from the tuberculum sellae to the occipital point.

Arnold Appleby

224. Spinal Intra-osseous Venography -

I. ISHERWOOD. *Clinical Radiology* [Clin. Radiol.] 13, 73-82, Jan., 1962. 14 figs., 24 refs.

After a detailed description of the anatomy and physiology of the vertebral and azygos venous systems the author discusses the possible methods of their demonstration, and proceeds to describe the technique of spinal intra-osseous venography practised at Manchester Royal Infirmary. After premedication and the taking of control films of the spine to demonstrate the inclination of the spinous processes, an iliac-crest bone-biopsy needle, Size 17, is introduced into a lumbar or dorsal spinous process under local anaes-

thesia. It is important to penetrate a spinous process only once during the examination since otherwise the contrast material will escape. Heparinized saline solution is then injected and a test-injection given of 5 ml. of 45% "hypaque", a lateral film being taken to establish the position of the needle. The main amount (20 ml.) of medium is then injected rapidly by hand and 3 or 4 serial films exposed at intervals of 1 or 2 seconds.

The technique may be useful in visualizing veins draining a spinal haemangioma, and in demonstrating obstructive lesions of the spinal canal. It may also be used to outline the inferior vena cava, to demonstrate the collateral circulation in portal hypertension, and to outline the azygos vein and thus determine how much it was contributing to an abnormal opacity in cases of suspected mediastinal lesion.

D. E. Fletcher

225. Patterns of Bone Change in Classic Hemophilia and Christmas Disease

J. E. MOSELEY. *Journal of the Mount Sinai Hospital* [J. Mt Sinai Hosp.] 29, 5-37, Jan.-Feb., 1962. 27 figs., 16 refs.

Diseases due to defects of blood coagulation are first briefly reviewed in this paper from the Mount Sinai Hospital, New York. Changes in the skeleton are essentially observed only in those due to deficiency of antihæmophilic globulin (classic hæmophilia) and of plasma thromboplastin component (Christmas disease). Such changes cannot be differentiated radiologically. Symptoms usually begin in infancy and tend to be most severe before puberty. They are associated with hæmorrhage, which may be subcutaneous, intramuscular, intra-articular, or internal, and is considered to be traumatic rather than spontaneous, even though a history of minimal trauma may not be obtained. The radiological patterns of bone change depend on the site, amount, and frequency of bleeding and especially also on the age at which these occur.

Intra-articular hæmorrhage may affect any joint, but the knee is particularly susceptible; most commonly it is the first joint to be involved and usually in infancy. Initially only a soft-tissue shadow indicative of joint distension is seen. Later repeated episodes result in subchondral cystic degeneration, eburnation of the articular surfaces, hyperæmic enlargement, and increased translucency of the epiphyseal centres, with widening of the intercondylar notch. Other joints are also involved and irregular enlargement of the head of the radius is a feature which should suggest the diagnosis. The epiphyses themselves develop a coarse vertical striation. Later in life the formation of areas of cystic degeneration, much more numerous than in other arthropathies, with reactive sclerosis and secondary osteoarthritis, may be expected.

Intra-osseous hæmorrhage, sometimes considered to be responsible for juxta-articular cystic change, may cause large lytic lesions, not only in the long bones but also in the flat bones. These, particularly in the femoral heads, are likely to induce collapse and evidence of avascular necrosis.

Subperiosteal hæmorrhage is not common, although a periosteal reaction along the shaft of a long bone may be

seen adjacent to an affected joint and be attributable to hyperaemia. When it does take place it is characterized by gradual calcification of the haematoma, deposition of periosteal new bone, and eventual resolution, possibly with slight residual cortical thickening. If, however, sufficient pressure is exerted on the adjacent cortical bone to result in bone resorption, the appearance may resemble that of a sarcoma, particularly since bony spicules tend to form within the haematoma and the margins of the lesion are likely to resemble the periosteal cuffing considered characteristic of a malignant tumour. These lesions, known as haemophilic pseudotumours, are seen commonly in the femur, but extensive destruction with an associated haematoma is well recognized in the iliac bones. Differentiation is important and may on occasion be made by the radiologist. The presence of haemophilic arthropathy of adjacent joints may be of great diagnostic value.

R. O. Murray

226. Pulmonary Changes in Cystic Fibrosis of the Pancreas: a Radio-pathological Study

C. J. HODSON and N. E. FRANCE. *Clinical Radiology* [Clin. Radiol.] 13, 54-61, Jan., 1962. 18 figs., 2 refs.

In 48 patients with cystic fibrosis of the pancreas studied at the Queen Elizabeth Hospital for Children, London, the authors have correlated the radiological and pathological features of the pulmonary changes and describe the following seven types of change. (1) In infants, collapse and emphysema due to severe, asphyxiating, obstructive bronchitis with formation of mucus plugs. (2) Thickening of the bronchial wall, which can be seen on tomograms and on plain chest films. (3) The presence of single or multiple discrete opacities anywhere in the peripheral lung field, rather similar to tuberculous lesions in the adult; these may appear and disappear and are thought to be due to small abscesses or bronchiectatic cavities. (4) Bronchiectasis, particularly the "scattered blob" variety due to staphylococcal infection. (5) Slight enlargement of the hilar lymph nodes when severe infection is present. (6) Persisting segmental atelectasis. (7) Cavities within areas of consolidation which persist as thin-walled cysts; these were seen in 2 cases. The effects of treatment on these various conditions are discussed.

D. E. Fletcher

227. The Jet Sign in the Angiocardiographic Diagnosis of Anomalous Pulmonary Venous Drainage

I. STEINBERG and D. S. LUKAS. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 294-307, Feb., 1962. 10 figs., 17 refs.

Refinement in the diagnosis of anomalous pulmonary venous drainage has become important now that surgical correction of the lesion is possible. From the New York Hospital-Cornell Medical Center, New York, the present authors describe a distinctive "jet sign" in the angiocardiogram at the site of the anomalous pulmonary venous insertion caused by turbulence of the contrast medium in contact with the unopacified blood from the pulmonary vein. Their observations are based on the study of a total of 19 such cases.

The majority of the filling defects visualized during angiocardiography are due to abnormal mixing of the medium with unopacified blood from either a cardiac chamber or vessel. Usually the head of pressure is greater in the unopacified structure and as a result a jet-like effect is pro-

duced in the opacified structure where there is blood flow through the defect. The jet sign associated with pulmonary venous drainage into the superior vena cava may be difficult to distinguish from the filling defects usually produced by the inflow of unopacified blood from the opposite innominate or the azygos vein. Generally these defects are less well defined, more transient, and smaller than those due to anomalous pulmonary veins. Later, when the anomalous pulmonary vein becomes opacified, it may be traced to the site of entrance; similarly, reflux filling may help in diagnosis. Pulmonary veins inserted at the junction of the superior vena cava and right atrium give a characteristic triangular filling defect, but it may be impossible to differentiate between filling defects in the right atrium due to large atrial defects and those caused by anomalous pulmonary veins. When anomalous pulmonary veins are inserted into the left innominate vein there is a clearly defined filling defect and the opacified vein can be easily visualized, though it is important in such cases to make the injection into the left arm. The demonstration of a filling defect in the right atrium due to complete insertion of the pulmonary veins into the coronary sinus is of considerable importance as it is difficult to differentiate drainage at this site from drainage into the right atrium.

The authors conclude that the jet sign is a more reliable indication of anomalous pulmonary venous drainage than is the passing of a catheter into the pulmonary vein. Unless oblique and lateral views of the chest are obtained with the catheter *in situ*, passage through the left atrium may not be recognized.

John H. L. Conway-Hughes

228. Sequestration of the Lungs and the Cardophrenic Angle. (Die Lungensequestration und die Herzwerchfellwinkel)

J. WELLAUER. *Radiologe* [Radiologe] 2, 74-81, Feb., 1962. 20 figs., 28 refs.

Sequestration of the lung is a developmental anomaly. The blood supply of the sequestered tissue is derived from an anomalous branch of the descending aorta, whereas drainage is by the pulmonary veins. The sequestered area is maldeveloped, devoid of its normal function, and frequently cystic. The condition is more often seen on the left side. The x-ray appearances vary greatly according to whether the sequestration is linked to the bronchial tree or not. If the latter, one or more solid, well-defined shadows may be seen. If there is communication with the bronchial tree, cyst-like cavities are found which can be filled by the contrast medium.

F. M. Abeles

229. The Roentgen Image of the Subclavian Artery in the Pulmonary Apex

B. GONDOS. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 86, 1058-1062, Dec., 1961. 6 figs., 13 refs.

From a review of 300 normal chest radiographs the author, writing from the General Hospital, Washington, D.C., claims that the shadow of the subclavian artery can be detected in 40% of cases. It presents as a faint, curvilinear opacity, more commonly on the left side, passing across the second or third posterior intercostal space. On the left side the shadow is continuous with the ascending portion of the subclavian artery, which forms the mediastinal border. On the right side the shadow springs from that of the

innominate vessel and appears a little higher. Verification of the nature of this shadow is provided by comparing cases in which calcification in the vessel accurately delineates its course. Tomography also usually serves to display the shadow clearly in the anterior sections of the apex. These, the author considers, are more reliable means of identification than angiocardigrams.

[The illustrations are of poor quality and not very helpful.]

A. M. Rackow

230. Cinefluorography of Coronary Artery Calcification: Correlation with Clinical Arteriosclerotic Heart Disease and Autopsy Findings

A. LIEBER and J. JORGENSEN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 86, 1063-1072, Dec., 1961. 4 figs., 19 refs.

The authors, at the Veterans Administration Hospital, Minneapolis, examined fluoroscopically 630 patients with heart disease of various types and 60 symptomless controls. A cine record was taken from the screen, employing image intensification. Routine scanning of the heart shadow in six standard sequences was designed to display the three main coronary vessels—the anterior descending and circumflex branches of the left coronary and the right main coronary artery. Necropsy studies revealed that where coronary calcification was detectable in the cine film a considerable degree of coronary atheroma existed.

It was found that there was an incidence of approximately 25% of coronary calcification both in patients with cardiac disease and in the controls when averaged over the 40 to 79 years age range. In both groups the peak incidence occurred in the 60 to 69 age group. Taking the group with calcification (150 patients) and comparing these with 80 patients who did not show calcification the authors found that a substantially higher proportion of the former displayed clinical evidence of arteriosclerotic heart disease. A correlation was observed between the number of branches involved by calcification and the degree of ischaemic heart disease clinically manifest.

It is concluded that while the presence of visible calcification in coronary vessels does not by itself imply existing cardiac disease, it may prove to be an indication of its incipient onset.

A. M. Rackow

231. The Use of Percutaneous Transfemoral Aortography to Diagnose Abnormalities of the Renal Arteries

J. M. STOKES and E. CARLSSON. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 276-283, Feb., 1962. 9 figs., 9 refs.

In this paper from Washington University School of Medicine, St. Louis, Missouri, the authors describe their technique of serial percutaneous transfemoral aortography, using the Seldinger needle, for the purpose of diagnosing renal arterial and aortic diseases associated with hypertension. The area over the common femoral artery is cleansed and a local anaesthetic injected. Both walls of the artery are punctured and the stylet removed. The open end of the needle is then pulled back into the femoral artery. The middle part of the needle is removed and the cannula inserted about 3 cm. proximally up the artery. The stylet is then replaced and a guide wire introduced a few centimetres into the artery and the needle removed. The artery should be compressed to prevent bleeding until the poly-

ethylene tube is inserted. The guide wire is removed when 5 or 6 cm. of the tube are in the artery. The polyethylene tube is then pushed up into the abdominal aorta. The tube is removed after arteriography and pressure is maintained over the puncture site for 5 minutes. The position of the tip of the catheter is ascertained by fluoroscopy after injection of a small quantity of the opaque medium. The tip should be left at the level of the renal arteries. The authors use between 20 and 40 ml. of 50% "hypaque" (sodium diatrizoate), 20 films being exposed in a Schönander film changer at a rate of 4 per second for 2 seconds and then 2 per second for 6 seconds. No serious bleeding or haematoma formation has been encountered and the technique has proved successful in children over the age of 11 years without the usual operative exposure of the artery.

The authors are of the opinion that renal arteriography should be carried out on every patient before removal of a kidney for unilateral arterial or parenchymal disease. Translumbar aortography has been widely used for investigation of the renal arteries, but it is accompanied by a significant incidence of complications. In contrast, the Seldinger technique has been used on 100 patients without any serious complications.

John H. L. Conway-Hughes

232. Transverse Tomography of the Heart and Great Vessels. (Die Transversalschichtuntersuchung des Herzens und der grossen Gefässe)

H. GREMMEL. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 3-36, Jan., 1962. 41 figs., bibliography.

In the method of performing transverse tomography of the heart and great vessels, as here described from the Medical Academy, Düsseldorf, five transverse sections are necessary. The first section, which is level with the 4th-5th thoracic vertebral interspace, shows the aortic arch, the trachea, and the superior vena cava. In the next section, at the level of D5-6, both main bronchi are seen, the aorta is shown separately in its ascending and descending portions, and the left pulmonary artery becomes visible. The third section, at the level of D7, reveals both trunks of the pulmonary artery. In the fourth cut, at the level of D8, all heart chambers contribute to the silhouette. The fifth and last cut is level with D9 and shows the notches between the right auricle and ventricle and between the right and left ventricles; in the majority of conditions this last cut yields most information. The tomographic appearances in various congenital and acquired heart lesions are analysed in detail.

F. M. Abeles

233. Assessment of the Degree of Mitral Incompetence by Selective Left Cardioangiography. (Graduelle Beurteilung der Mitralklappeninsuffizienz im selektiven Laevokardiogramm)

P. THURN, A. SCHAEDE, H. H. HILGER, and A. DÜX. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 37-60, Jan., 1962. 12 figs., bibliography.

In this communication from the University of Bonn the authors show how, by means of selective left cardioangiography, the degree of incompetence of the mitral valve can be assessed by (1) the density and extent of the retrograde filling of the left auricle (part of the whole of the left atrium may show retrograde filling); (2) the time relationship be-

tween the retrograde filling of the left auricle and the aorta; (3) the emptying time of the left heart chamber, best determined by relation to the number of heart beats; (4) the degree of dilatation of the left ventricle (but not of the auricle); and (5) the flushing backwards of the catheter tip. They have found that the reflux sometimes goes as far back as the pulmonary veins. By this technique it is also possible to decide the exact location of the valvular leak, that is, whether it is antero-lateral or postero-medial.

F. M. Abéles

RADIOTHERAPY

234. **The Determination of the Radio-sensitivity of Tumours**
P. A. BROWNE. *Irish Journal of Medical Science* [*Irish J. med. Sci.*] 6, 475-486, Nov., 1961. 2 figs., 9 refs.

In this study reported from the Royal College of Surgeons of Ireland, 16 patients with advanced breast carcinoma (tumour immediately beneath the skin) and 4 patients with squamous carcinoma of the skin were given 500 μ c. of radioactive phosphorus (^{32}P) by mouth before radiotherapy. Daily counts were made during treatment over precisely located areas in each case and the counts were corrected for decay of the ^{32}P . On the assumption that the amount of ^{32}P present at any time is an index of the number of mitoses occurring, the author believes that an early assessment of the radiosensitivity of the tumour and of the prognosis of the case can be obtained.

[A table is provided for the cases of carcinoma of the breast showing the prognosis ("good", "fair", or "poor") as determined by this method and the clinical results of subsequent treatment, agreement between the two being claimed in all of the 10 cases in which prognosis could be accurately estimated and the patient survived long enough for the clinical result to be judged. However, the lack of much essential information makes it difficult to assess the validity of the author's claims. For example, no details are given of the amount of radiotherapy the patients received or of the rate at which it was given and there are no physical details about the type of counting apparatus used.]

E. Stanley Lee

235. **Radiation Therapy of Lesions Overlying Cartilage.**
I. **Carcinoma of the Pinna**

R. G. PARKER and O. WILDERMUTH. *Cancer* [*Cancer (Philad.)*] 15, 57-65, Jan.-Feb., 1962. 9 figs., 13 refs.

In the provision of the greatest therapeutic ratio, which must be the aim of radiation therapy, certain factors can be controlled. The tissue underlying the tumour cannot be controlled, but it is within the limits of influence through technique. Problems result when cartilage underlies a tumour or is in its proximity, for example, in the ear, nose, throat, larynx, or lung. Cartilage is relatively insensitive to irradiation, although damage can be produced by this agent as by other agents. This damage may not declare itself for several years and then often in association with trauma or infection. Such functionally compromised tissue may be undetectable by ordinary histology. Repair of cartilage after injury is sluggish. A defect is filled in by fibrous tissue and new cartilage is formed by metaplasia of this. Proximity of a tumour to, or its invasion of, cartilage is considered by many radiologists to be a contraindication to radiation therapy; others however consider that with

special adaptation of techniques this need present no major difficulty. This study was carried out at the University of Washington, Seattle, to try to clarify this problem, and was concerned with carcinoma of the pinna.

Out of 77 patients referred during the period 1940-57, 37 patients (39 lesions) were irradiated with 120 to 140 kV., H.V.L. 1 to 3 mm. Al. Doses varied from 3,500 r. in 10 days to 6,000 r. in 6 weeks. All early lesions were controlled and even in some advanced lesions palliation was obtained. Surgical resection of the pinna is usually effective and functionally satisfactory, but the cosmetic result is not always acceptable. Meticulous radiation therapy of lesions of the pinna can be as effective as resection, with a less objectionable end-result than after surgery and the treatment need not result in any significant morbidity. Moreover, even if irradiation fails or causes morbidity subsequent surgical resection is not prejudiced.

I. G. Williams

236. **Clinical Trial of a Modified ("Split-course") Technique of X-ray Therapy in Malignant Tumours**

D. K. SAMBROOK. *Clinical Radiology* [*Clin. Radiol.*] 13, 1-12, Jan., 1962. 1 fig., 26 refs.

Writing from the Swansea and West Wales Hospitals, the author describes a modified method of extended fractionation of x-irradiation—the "split-course" technique—whereby treatment is stopped short of producing a troublesome reaction, that is, between 2,000 and 3,000 r., in the second or third week. This is followed by a "rest" period of 2 to 4 weeks during which continued regression of the tumour is often seen, accompanied by healing of normal tissues. Treatment is then resumed to a similar dosage as before, the factors being 250-kV. x rays, H.V.L. 1.5 mm. Cu, given in equal daily fractions. The author suggests that the "split-course" technique may use to greater advantage than does conventional fractionation the differential recovery rates of normal and tumour tissues; also the blood and oxygen supply of the tumour may improve during the rest period and so increase the radiosensitivity of the tumour. These and other possible theoretical benefits of the method are discussed.

The author then reports a clinical trial of the method, carried out on patients many of whom were elderly and frail and most of whom had advanced neoplasm, in some cases with distant metastases. The period of observation was short and so assessment is essentially of the local result rather than of length of survival. The lesions were mostly epidermoid carcinoma of the head and neck region. Of 28 patients with carcinoma of the tongue and mouth 17 showed a good response; of 21 with cancer of the laryngo-pharynx or hypopharynx control of the tumour was obtained in 11; of 11 with glottic carcinoma and 17 with postcricoid tumour good results were obtained in 9 and 4 respectively, while 3 patients with advanced nasopharyngeal growths all responded well. Of 9 patients with bronchial carcinoma, 6 obtained almost complete relief of symptoms for over 6 months following treatment, and healing was also achieved in 3 very advanced cases of breast tumour by this method. It is stated that control of the disease within the treated volume was obtained in just over one-half of 92 patients with advanced tumour.

Only 11 patients had severe reactions and usually the reaction was less than would have been expected with conventional methods.

W. Duncan

ABSTRACTS OF WORLD MEDICINE

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Pathology

237. An Experimental Study of the Pathological Effects of Cigarette Condensate in the Lungs with Special Reference to Carcinogenesis

J. W. S. BLACKLOCK. *British Journal of Cancer* [Brit. J. Cancer] 15: 745-762, Dec., 1961 [received March, 1962]. 34 figs., 42 refs.

Although the results of keeping animals in an atmosphere of cigarette smoke have been varied, the condensate of cigarettes has been shown to produce malignant tumours in the lungs of a small number of rats and, when painted repeatedly on the skin, of mice and rabbits. In this paper the author reports from St. Bartholomew's Hospital, London, the histopathological changes in the lungs of rats, guinea-pigs, and rabbits resulting from the direct introduction, by thoracotomy, of the cigarette condensate from about 40 cigarettes prepared in a smoking machine and suspended in the oily cream "eucerin", as well as the results of similar inoculations in a pure strain of rats which were allowed to live until death. The condensate contained 4 μ g. of 3:4-benzopyrene per 500 cigarettes. In those rats in which the inoculated condensate penetrated into the bronchial system the ciliated epithelium was quickly destroyed and this was followed, in order of time, by proliferation of the basal cells, squamous metaplasia, papilloma formation, hyperplasia of the squamous epithelium giving rise to an appearance not unlike "carcinoma *in situ*" in man, and finally in one instance (570 days after the inoculation) to a definite squamous epithelioma. No such epithelial changes were produced in control rats by eucerin alone. Phagocytosis of small particles of the condensate was frequently observed, while between weeks 53 and 104 there was evidence that in some bronchi the metaplastic changes in the epithelium were being reversed. Similar changes were observed in the lungs of the guinea-pigs and rabbits, but in these species no definite epithelioma developed.

In the second series of experiments a malignant lung tumour developed in 8 (11.1%) of 72 rats inoculated with the cigarette condensate, whereas in the 44 control animals inoculated with eucerin alone only one (2.3%) developed a malignant tumour; in the same period, of a group of 275 untreated rats 4 (1.4%) developed spontaneous malignant pulmonary tumours. In the experimental group 6 of the 8 tumours were carcinomata, composed of undifferentiated cells possibly derived from the basal cells, and 2 were sarcomata; with one exception, the tumours in the control groups were all sarcoma. In all groups most of the neoplasms occurred between 18 and 21 months, but in the period up to 15 months only malignant tumours associated with cigarette condensate occurred.

These experiments show that cigarette condensate can produce malignant tumours in the lungs of rats. The author

suggests that the amount of 3:4-benzopyrene in the cigarette condensate would seem to be too small to exert a direct carcinogenic effect, so possibly an unknown carcinogen is formed during pyrolysis, since extracts of unburned tobacco or purified nicotine have been found to have no carcinogenic properties. The present results seem to indicate that tobacco condensate has to be in contact with the tissues of the lungs for a long time before exciting a neoplastic response. In the human subject, if the ciliated epithelium has been destroyed by disease by living in a highly polluted urban atmosphere or by habitual cigarette smoking, inhaled particulate matter would be liable to be retained and any chronic peribronchial inflammation might cause a focal accumulation. If several types of particles had carcinogenic powers, one might exert a co-carcinogenic effect on the weak carcinogen which cigarette smoke appears to be.

A. Ackroyd

238. Endogenous Creatinine Clearance: a Valuable Clinical Test of Glomerular Filtration and a Prognostic Guide in Chronic Renal Disease

G. J. TOBIAS, R. F. McLAUGHLIN JR., and J. HOPPER JR. *New England Journal of Medicine* [New Engl. J. Med.] 266: 317-323, Feb. 15, 1962. 1 fig., 34 refs.

The clinical significance of the endogenous creatinine clearance value in chronic renal disease was studied at the University of California School of Medicine, San Francisco, this value being determined in substantial numbers of healthy subjects and patients suffering from the disease. Determination of the clearance value was found to be superior to simple determination of the serum creatinine level, with which it was only very roughly correlated. As a practical procedure, it was much more useful than estimation of the inulin clearance, and repeated determinations could conveniently be made. Superimposed hypertension led to sharp decreases in creatinine clearance; at any given level of depressed creatinine clearance the patient's survival was critically affected by the degree of hypertension present.

D. A. K. Black

239. Studies on Platelet Antibodies in Man. [In English] T. W. M. VAN DE WIEL, H. VAN DE WIEL-DORFMEYER, and J. J. VAN LOGHEM. *Vox sanguinis* [Vox Sang. (Basel)] 6: 641-668, Nov., 1961 [received Feb., 1962]. Bibliography.

At the Netherlands Red Cross Blood Transfusion Service, Amsterdam, the authors have used several techniques for the detection of platelet antibodies in patients with various blood diseases and in normal control subjects; they also studied patients who had received multiple blood transfusions. In addition to direct tests for the presence of complete platelet antibodies they used the anti-human-globulin consumption (A.H.G.C.) test and a complement fixation

test. All these techniques require minute attention to detail if comparable results are to be obtained; the techniques are fully described and discussed. Platelet function was further tested by thromboelastography.

The sera of 406 patients who had received blood transfusion gave positive results by the agglutination test in 22 cases, by the A.H.G.C. test in 58, the complement fixation test in 18, and thromboelastography gave an abnormal result in 22. Positive results were recorded more often in patients who had had many transfusions. Positive results with the sera of 69 patients with idiopathic thrombocytopenia were obtained with the agglutination test in 5 cases, the A.H.G.C. test in 8, and the complement fixation reaction in 2; the corresponding numbers of positive results in a group of 352 patients with secondary thrombocytopenia due to various diseases were 21, 31, and 9 respectively. Figures are also given for the results of the direct A.H.G.C. test on the platelets; thus positive results were obtained in 13 of 23 patients with idiopathic thrombocytopenia, in 22 of 81 patients with secondary thrombocytopenia, and in 7 out of 56 patients with blood diseases but no thrombocytopenia; no positive results were obtained in 581 normal subjects. Thromboelastography was carried out in some of these patients, but the results did not correlate with the other tests.

It is concluded that these studies show that the A.H.G.C. test is the best for the detection of platelet autoantibodies and isoantibodies, the complement fixation test being less sensitive for the recognition of autoantibodies. The results do not indicate clearly whether platelet antibodies are the primary cause of thrombocytopenia or whether their presence only aggravates the effect of lack of platelets.

M. C. G. Israëls

MORBID ANATOMY AND CYTOLOGY

240. An Evaluation of Methods of Inducing Sputum Production in Patients with Suspected Cancer of the Lung
R. S. FONTANA, D. T. CARR, L. B. WOOLNER, and F. K. MILLER. *Proceedings of the Staff Meetings of the Mayo Clinic* [Proc. Mayo Clin.] 37, 113-121, Feb. 28, 1962. 1 fig., 10 refs.

Two methods of inducing sputum production were tried at the Mayo Clinic in a series of 201 patients with suspected carcinoma of the bronchus who could raise little or no sputum. In the first method patients were given inhalations of a heated aerosolized solution of saline and propylene glycol and in the second method an aerosolized solution of sulphur dioxide. The former was preferred because it produced a greater volume of secretion. Although both methods were found to be useful, the authors consider that further improvement in present techniques of inducing, processing, and examining sputum should be attempted.

J. B. Wilson

241. Mineralising Elastosis in Blood Vessels in Resected Lungs from Patients Undergoing Prolonged Chemotherapy
I. M. GUPTA. *Journal of Pathology and Bacteriology* [J. Path. Bact.] 83, 13-20, 1962. 13 figs., 25 refs.

The author, working at the University of Delhi, has previously (*Indian J. Chest Dis.*, 1961, 3, 1) pointed out the unusual histological appearances to be seen in the blood vessels of the lungs of certain patients who have had prolonged chemotherapy for tuberculosis. He has called this

"mineralizing elastosis" and the present paper deals with this in greater detail.

Sections from 92 resected lungs have been studied with special attention to the blood vessels, from 4 to 6 sections taken at random from the diseased areas being examined from each specimen. Eight specimens showed mineralizing elastosis and all these patients had had streptomycin, PAS, and isoniazid in different combinations and for different periods of time. Seven of them were suffering from pulmonary tuberculosis and one from cystic bronchiectasis. In none of the other patients, who had received no anti-tuberculous drugs, could mineralizing elastosis be demonstrated in the lungs.

Focal calcification in the vessel wall was the outstanding pathological change in the vessels of the 8 lungs showing mineralizing elastosis. In the large and medium-sized branches of the pulmonary artery calcium salts were deposited selectively in the elastic fibres of the media, which appeared degenerated and often refractile. In the large veins the calcium deposition was intimal. Some of the vessels showed inflammatory infiltrates, particularly in areas where the fibres were fragmented. Such cellular infiltrates invariably included eosinophils with lymphocytes and a few polymorphonuclear leucocytes.

Thus although there is no conclusive evidence that mineralizing elastosis in blood vessels is related to the administration of antituberculous drugs, the author suggests there is need for further study of this subject. Special attention to the blood vessels of such lungs, particularly in the hilar region, may reveal the presence of this pathological change with greater frequency.

G. Clayton

242. Gastric Tissue Changes in Association with Gastric Ulcer

E. DEUTSCH, H. J. CHRISTIAN, and R. FABREGAS. *American Journal of Gastroenterology* [Amer. J. Gastroent.] 37, 168-173, Feb., 1962. 2 figs., 3 refs.

A 10-year study of the histological changes in the gastric mucosal environment in 89 patients with proven gastric ulcer is reported from Tufts University Medical School and Carney Hospital, Boston. The ages of the patients (48 male and 41 female) ranged from 22 to 81 years (average 51 years). Multiple gastric biopsy specimens were examined by light microscopy. In 8 (9%) of the cases there was marked inhibition or absence of healing of the ulcer, in spite of thorough medical treatment. All these 8 patients had severe chronic gastritis. In the remaining 81 patients in whom the mucosal environment was normal or gastritis was mild or moderate, ulcer healing occurred completely in 3 to 6 weeks. It is concluded that the association of severe chronic gastritis with a chronic gastric ulcer is an indication for surgical treatment of the latter.

A. Wynn Williams

243. A Study with the Electron Microscope of the Jejunal Epithelium in Primary Malabsorptive Disease

D. J. C. SHEARMAN, R. H. GIRDWOOD, A. W. WILLIAMS, and I. W. DELAMORE. *Gut* [Gut] 3, 16-25, March, 1962. 13 figs., 18 refs.

A study under the electron microscope of the jejunal mucosa in primary malabsorptive disease is reported from the University and Royal Infirmary, Edinburgh. Biopsy specimens were obtained by means of the Crosby capsule from one healthy adult and 7 adults with malabsorptive

disease. In 3 of the 5 patients with "primary" malabsorptive disease, the mucosal pattern was abnormal under the light microscope and under the electron microscope the microvilli appeared sparse, stunted, and broadened. In the remaining 2 patients the appearances under the light microscope and the microvilli were normal. Primary malignant disease of the small bowel was present in 2 patients. In one of these, with anaplastic carcinoma, the appearances of the mucosal specimen under the light microscope were abnormal but there were normal-looking microvilli. In the other patient, who had reticulum-celled sarcoma, both the villi and microvilli were abnormal. This study illustrates the value of jejunal biopsy and microscopy in the diagnosis of primary malabsorptive disease and indicates the present limitations of these procedures.

A. Wynn Williams

244. **Studies on Chronic Glomerulonephritis. I. The Fine Structure of the Intracapillary Alterations of the Glomerulus** J. W. STEINER, H. Z. MOVAT, E. R. YENDT, and R. J. SLATER. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 153-167, Jan. 27, 1962. 23 figs., 15 refs.

The intracapillary changes in chronic glomerulonephritis are analysed in this paper from the University and the Hospital for Sick Children, Toronto. A total of 25 needle biopsy specimens of the glomerulus from patients in whom chronic glomerulonephritis had been diagnosed clinically were examined. The tissues were fixed, dehydrated, and embedded in methacrylate, and were examined, unstained or after staining, under the electron microscope.

The authors describe the fine structural alterations observed in the glomerulus as follows. (1) A thickening of the lamina densa of the basement membrane. (2) Formation of deposits of material of distant electron microscopic appearance next to the basement membrane and between endothelial cells. The deposits are ultimately converted into a substance similar to the basement membrane. (3) Proliferation of the endothelial cells is evidenced by fusion of the fenestrated cytoplasm, layering of cytoplasmic processes, villous or massive hypertrophy of the main cell mass and formation of reticulated projections of the cytoplasm. (4) The axial reaction consists of hyperplasia and hypertrophy of these cells together with increase in size of existing and formation of new basement membrane anchors. (5) All these processes contribute to the gradual narrowing of capillary lumina and to the resulting glomerular obsolescence.

It is stated that in a further paper these observations will be correlated with the light microscope findings and the whole study will form the basis "for a discussion of a concept of the morphogenesis of the intracapillary lesions of chronic glomerulonephritis".

G. Clayton

245. **Diabetic Glomerulosis: an Ultra-structural Study.** (La glomérulose diabétique: étude ultra-structurale) P. MERIEL, C. DARNAUD, Y. DENARD, G. MOREAU, J. M. SUC, J. PUTOIS, and P. F. COMBES. *Presse médicale* [Presse méd.] 70, 667-670, March 21, 1962. 9 figs.

At the Faculty of Medicine, Toulouse, the authors have examined histologically needle biopsy specimens of kidney from 40 diabetic patients, 13 of the specimens being also examined by electron-microscopy.

The most characteristic changes were found in the glomerular basement membrane, which was thickened up to 10 times

its normal width and had developed concertina-like folding, though this folding was not limited to the thickened membranes. The endothelial cells were surrounded by hyaline material similar in appearance to the basement membrane but with ill-defined contour; in some specimens this had become very plentiful, compressing the nucleus and residual cytoplasm towards the capillary lumen, and occasionally causing complete stenosis thereof. The epithelial cells showed less constant changes. Bowman's capsule was thickened up to 10,000 Ångström units but retained its lamellar structure.

In some cases two other abnormalities, which however may be present in other diseases, were seen, namely, small vacuoles situated near the nucleus of epithelial cells, and structureless rounded bodies lying in the cytoplasm of epithelial cells; these latter bodies sometimes conglomerated to form a large spherical mass. The typical Kimmelstiel-Wilson nodule was difficult to study by electron-microscopy because of its size. However, it was possible to distinguish two parts: (1) the periphery, made up of long ribbons resembling the basement membrane and enclosing capillary cells, and (2) the centre, which consisted of hyaline material containing nuclear debris. The authors consider that the Kimmelstiel-Wilson lesion arises as a result of the coalescence of the thickened basement membrane and the hyaline deposits found in relation to the endothelial cells. They believe these changes are preceded by changes in the afferent arterioles and are continuous with them through changes in the intervening mesangium.

H. Caplan

246. **The Post-mortem Incidence of Focal Thyroiditis** E. D. WILLIAMS and I. DONIACH. *Journal of Pathology and Bacteriology* [J. Path. Bact.] 83, 255-264, 1962. 2 figs., 38 refs.

That microscopic foci of thyroiditis occur in surgical specimens of toxic and non-toxic goitre has been known for many years. Similar foci of thyroiditis have also been noted in post-mortem studies of the thyroid glands of patients dying of other diseases. The present authors have considered it worthwhile to add to these findings the results of a further large post-mortem study of thyroid glands to determine the incidence of focal thyroiditis and its correlation with other diseases, and to this end sections from 724 glands removed at necropsy over a period of 5 years at Hammersmith Hospital (Postgraduate Medical School of London) were therefore examined. Each section, 6 μ in thickness, was examined under the low power of the microscope and the number of foci per square centimetre counted, a collection of lymphocytes or plasma cells easily visible with the low power objective being the criterion for a focus of thyroiditis. Focal thyroiditis was present in 19% of glands from adult males and in 45% of those from adult females. In most cases it was of mild extent, but in 6% of males and 22% of females there was more severe involvement, over 10 foci per sq. cm. being found. There was a sharp rise in the incidence among females over the age of 50, the increase being almost entirely due to the milder form. No focal thyroiditis was found in any subject under the age of 22 years.

Using these findings as a basis the authors then examined a further series of thyroid glands in order to correlate the incidence of focal thyroiditis with other diseases. In 4 male and 18 female patients with pernicious anaemia and 22

females with idiopathic hepatic cirrhosis both incidence and severity were greater than was expected; thus in pernicious anaemia 9 cases were expected and 13 observed, while in the women with hepatic cirrhosis 10 cases were expected but 13 were observed. A similar increase in focal thyroiditis has been previously noted in primary Addison's disease. Diseases in which no increased incidence of thyroiditis was observed included rheumatoid arthritis (31 cases) and systemic lupus erythematosus (11). The authors conclude that if focal thyroiditis is accepted as an autoimmune manifestation, its association with other diseases suggests that it may represent more than a local reaction to release of tissue antigens. It could be regarded as a pointer to a more generalized weakening of immune tolerance in the patient. But this cannot at present be more than speculation until an autoimmune mechanism has been proved in those diseases with which it is associated. *G. Clayton*

247. Renal Venous Thrombosis of the Newborn and Its Relation to Maternal Diabetes: Report of 16 Cases. [In English]

A. TAKEUCHI and K. BENIRSCHKE. *Biologia neonatorum* [Biol. neonat. (Basel)] 3, 237-256, Sept. [received Dec.], 1961. 5 figs., 26 refs.

This is a report of renal venous thrombosis in 6 stillborn and 10 newborn infants from autopsy files [at the Lying-in and Beth Israel Hospitals, Boston, Massachusetts]. In one child the diagnosis was made during life but following nephrectomy the thrombosis spread to the other kidney. In all but one case the evidence favors the prenatal onset of the thrombotic process. In 5 instances maternal diabetes was present, in 7 others the likelihood of clinically unrecognized prediabetes is presented. The authors put forth a tentative hypothesis to account for the association with maternal diabetes in that they assume renal hemoconcentration incident to glycosuria. It is pointed out that renal vein thrombosis often occurs in the absence of gross pathologic lesions of the kidney. It is therefore a microscopic diagnosis, at least in the perinatal period.—[Authors' summary.]

248. Fatty Change in the Myocardium of the Newborn

J. M. SCOTT. *British Medical Journal* [Brit. med. J.] 2, 1746-1749, Dec. 30, 1961. 2 figs., 17 refs.

In this paper from the Glasgow Royal Maternity Hospital the author, noting the frequency of clinical signs and post-mortem features of cardiac failure in infants dying in the neonatal period, reports on the incidence of fatty change in the myocardium of infants dying in the perinatal period. Necropsy specimens from 57 neonatal deaths and 15 fresh stillbirths were examined, blocks from each side of the heart, including both atrium and ventricle, being stained for fat and glycogen. The cases were graded independently according to the amount of fat and glycogen present. Glycogen staining gave variable results, but a clearer pattern was evident on staining for fat. In general, fatty change appeared first in the right heart, was greater in the ventricle than in the atrium, and was never greater in the left than in the right heart.

The author tabulates the neonatal deaths and 6 of the stillbirths according to the final diagnosis of cause of death and incidence of fatty change. Of 21 cases with hyaline membrane, 19 showed post-mortem signs of cardiac failure and fatty change was present in 17. In the 11 cases in which

fatty change was most severe there was a general correlation between the amount of fat, duration of life, and extent of membrane. In the other 6, in which fatty change was less, the membrane was not so extensive, primary atelectasis was frequent, and death occurred earlier. The other groups were smaller, but it appeared that fatty change was more frequent in deaths due to asphyxia, haemolytic disease (this group included 4 stillbirths), or severe foetal anoxia, than in those due to haemorrhage or in stillbirths.

The author considers that the similar findings in hyaline membrane disease and asphyxia might be due to the common factor of atelectasis causing anoxia and increased cardiac effort due to pulmonary hypertension. She argues that these two factors might well occur more frequently in the other groups in which fatty change was more prominent than in those in which this feature was not conspicuous, and indicates a general correlation between clinical features suggesting cardiac stress, necropsy findings of cardiac failure, and fatty change in the myocardium. *E. G. Hall*

249. Neuropathological Observations on Cerebral Edema: the Acute Phase

I. FEIGIN and N. POPOFF. *Archives of Neurology* [Arch. Neurol. (Chic.)] 6, 151-160, Feb., 1962. 9 figs., 18 refs.

Until recently oedema of the brain was thought to resemble that of other organs in consisting of the accumulation of fluid in an extracellular space in addition to any intracytoplasmic changes.

Recent electron microscopic studies have been interpreted as indicating that such extracellular space is virtually non-existent except possibly for a relatively constant zone no larger than 200 Å. between adjacent cellular processes. In oedematous brain, electron microscope studies revealed swelling of cellular processes with a pale, clear cytoplasm. These pale cellular processes are thought to be those of oligodendroglial cells or of astrocytes, or have not been otherwise identified. In the light of these observations the authors working at New York University School of Medicine and Bellevue Hospital, New York, thought it necessary to review the gross and light microscopic changes in oedema of the brain to determine whether these were consistent with the concept suggested by electron microscopy.

Gross examination reveals minimal involvement of the cortex, with predominant involvement of the subjacent white matter. Many electron micrographs of the cortex reveal the swelling of the pale glial fibres, presumably astrocytic, thought to be the essence of cerebral oedema. A relative sparing of the arcuate zone of the white matter is seen in some cases. There is nothing in the distribution or morphology of the astrocytes in this zone which would distinguish them from those more deeply placed. The tangential orientation of the nerve fibres in this zone, however, might serve as a barrier to the spread of extracellular fluid. The quantity of fluid that may be present in oedematous white matter is of such magnitude as to render difficult its retention within the cytoplasmic limits of the astrocytes. An extracellular space could distend to a much greater degree.

The histological studies described in this paper suggest that an extracellular accumulation of fluid may be present, but this does not imply that intracellular changes such as those observed in electron micrographs do not occur.

J. MacD. Holmes

Microbiology and Parasitology

250. Recovery of New Viruses (Coryzavirus) from Cases of Common Cold in Human Adults.

V. V. HAMFARIAN, A. KETLER, and M. R. HILLEMANN. *Proceedings of the Society for Experimental Biology and Medicine* [Proc. Soc. exp. Biol. (N.Y.)] 108, 444-453, Nov., 1961 [received Feb., 1962]. 2 figs., 15 refs.

This preliminary report from the Merck Institute, West Point, Pennsylvania, describes the properties of an apparently new group of viruses isolated from cases of the common cold. The viruses were recovered from throat swabs by inoculation on tissue cultures of a strain of serially propagated human foetal fibroblasts of diploid karyotype, recently developed by Hayflick at the Wistar Institute. Viruses of this new group, provisionally named "coryzaviruses", were isolated from 17 of 110 subjects with the common cold and from one of 45 control subjects. One-third of the affected subjects complained of cough and of hoarseness but none of them had clinically significant fever.

Neutralization tests were performed with the homologous strain of coryzavirus on the paired sera from 10 of the persons from whom virus had been isolated, but in only 4 cases was an antibody response detected. The coryzaviruses produced a cytopathic effect on the fibroblast cultures (derived either from lung or kidney) usually within 2 to 5 days, in which rounding and lysis of the cells occurred with eventual destruction of the cell sheet. The viruses, as well as being readily isolated at 33° C., could also be propagated at 36° C., but no multiplication or cytopathic change was produced in either HeLa or grivet renal cell cultures, nor could these viruses be propagated in suckling or adult mice, guinea-pigs, or in chick embryos. There was no production of haemagglutinin. At least 6 serological types were distinguished, but none of these was related to two of the prototype "Salisbury" strains of rhinovirus isolated from common cold cases in England. No serological relationship could be demonstrated with E.C.H.O., Coe, Pett, or Reo viruses. In respect of particle size, ether resistance, and ribonucleic acid content, the coryzaviruses resemble the enteroviruses, but their precise relationship to this group and to the rhinoviruses remains to be elucidated.

J. E. M. Whitehead

251. Serotype of Viruses (Rhinoviruses) Isolated from Common Colds

D. TAYLOR-ROBINSON and D. A. J. TYRRELL. *Lancet* [Lancet] 1, 452-454, March 3, 1962. 1 fig., 7 refs.

This paper from the M.R.C. Common Cold Research Unit, Salisbury, Wilts, reports further progress in the serological analysis of the strains of virus isolated under certain cultural conditions from cases of the common cold and designated "rhinoviruses". The strains were examined by means of neutralization tests in which reduction of the number of plaques formed by the virus in roller tube cultures at 33° C. was measured, taking 50% reduction as the end-point. On the basis of cross-neutralization tests performed in this way 6 different viruses, 4 of which were H strains, that is,

they grew only in human embryo kidney, and 2 were M strains, that is, those which also grew in monkey kidney tissue cultures, were shown to be distinct from one another. None of them was neutralized by sera against E.C.H.O. viruses 1 to 28, Coxsackie A viruses 1 to 24, or Coxsackie B viruses 1 to 6, although some minor cross-reactions were observed with Coxsackie A 7 and E.C.H.O. 4 antisera. Seven further M strains were identical serologically with E.C.H.O. virus 28 (J.H. virus), while 3 strains remained unidentified with the sera used. Only one of the 8 further H strains was neutralized by antiserum against one of the new serotypes of rhinovirus. The authors also report that they were unable to demonstrate pathogenicity for suckling mice by intraperitoneal or intracerebral routes of inoculation with 4 H strains and 3 M strains. J. E. M. Whitehead

252. Rapid Presumptive Identification of Enteropathogenic *Escherichia coli* in Faecal Smears by Means of Fluorescent Antibody. 1. Preparation and Testing of Reagents

B. M. THOMASON, W. B. CHERRY, B. R. DAVIS, and A. POMALES-LEBRÓN. *Bulletin of the World Health Organization* [Bull. Wld Hlth Org.] 25, 137-152, 1961. 1 fig., 27 refs.

In view of the fact that during outbreaks of infantile diarrhoea it is essential, in order to ensure specific and adequate treatment, to identify the responsible organism as soon as possible, the authors of this paper from the Communicable Disease Center, Atlanta, Georgia, have investigated the value of the fluorescent antibody technique of Whitaker *et al.* (*Amer. J. Dis. Child.*, 1958, 95, 1; *Abstr. Wld Med.*, 1958, 24, 87) for the rapid identification of serotypes of *Escherichia coli*. For this purpose, the OB antibodies of 9 such serotypes were obtained from rabbits, globulin solutions prepared by precipitation with ammonium sulphate, and these then labelled with fluorescein isothiocyanate. Test on cultures of the different *E. coli* serotypes and various species of *Salmonella* and *Shigella* showed that the fluorescent antibody test was specific, there being little or no tendency to cross reactions. R. Hare

253. Rapid Presumptive Identification of Enteropathogenic *Escherichia coli* in Faecal Smears by Means of Fluorescent Antibody. 2. Use of Various Types of Swabs for Collection and Preservation of Faecal Specimens

B. M. THOMASON, W. B. CHERRY, and A. POMALES-LEBRÓN. *Bulletin of the World Health Organization* [Bull. Wld Hlth Org.] 25, 153-158, 1961. 3 figs., 12 refs.

Although for the identification of enteric pathogens culture of faecal specimens as soon as possible after collection from the patient is obviously desirable, it may occasionally be necessary to preserve them for some time. Since collection of the specimens in buffered glycerol saline solution renders them unsuitable for examination by fluorescent antibody techniques, an alternative method was sought and in this study the feasibility of their collection on rectal swabs was investigated. Swabs made of either cotton or "dacron" were shown to be equally satisfactory, but freezing after collection in order to preserve the organisms was

found to be inadvisable. If, however, the faeces were allowed to dry on the swabs at room temperature, serotypes of *Escherichia coli* survived for several weeks and could be detected by both culture and fluorescent antibody methods at the end of that time.

R. Hare

254. Rapid Presumptive Identification of Enteropathogenic *Escherichia coli* in Faecal Smears by Means of Fluorescent Antibody. 3. Field Evaluation

W. B. CHERRY, B. M. THOMASON, A. POMALES-LEBRÓN, and W. H. EWING. *Bulletin of the World Health Organization* [Bull. Wld Hlth Org.] **25**, 159-171, 1961. 12 refs.

In this third study [see Abstracts 252 and 253] the value of the fluorescent antibody technique for the detection of pathogenic serotypes of *Escherichia coli* in faeces was investigated in parallel with conventional culture methods involving isolation and identification by slide agglutination. Rectal swabs were obtained from 291 cases of diarrhoeal disease in children living in Puerto Rico. In 72 of these one of the several *E. coli* serotypes could be identified both by the fluorescent antibody method and by culture. A further 34 were found to have serotypes which reacted with the fluorescent antibody but which could not be detected by cultural methods.

The authors suggest that the probable reason for this apparent discrepancy was that cultures were carried out immediately after the specimen was taken, whereas there was considerable delay before the smears for study by the fluorescent antibody technique were prepared. During this period the swabs were held at room temperature, which enabled the organisms to multiply and so become sufficiently numerous to be detected by the fluorescent antibody method.

R. Hare

255. Concentrations of Fungus Spores in the Air Inside a Cattle Shed [In English]

T. SREERAMULU. *Acta allergologica* [Acta allerg. (Kbh.)] **16**, 337-346, 1961. 2 figs., 7 refs.

Over a period of one month a survey was carried out of the air spora in a cattle shed on a dairy farm in India, a Hirst automatic volumetric spore trap being used. Spores of *Cladosporium* and *Fusarium* accounted for 48.3% and 27.0% respectively of the total catch. Basidiospores and *Aspergilli* type contributed 8.3% and 3.2%. The daily maximum concentration of *Cladosporium* occurred during the middle of the day, while that of the *Aspergilli* type occurred during the afternoon. The diurnal periodicities could be related to some extent to certain operations, such as feeding of the cattle. Details are given of the highest daily mean concentration, the highest hourly concentration, and the highest hourly mean concentration observed for each of the spore types.

A. W. Frankland

256. Immunological Studies of Measles

J. STOKES JR., C. M. REILLY, E. B. BUYNACK, and M. R. HILLEMANN. *American Journal of Hygiene* [Amer. J. Hyg.] **74**, 293-303, Nov., 1961. 4 figs., 14 refs.

This paper from the School of Medicine, University of Pennsylvania, the Children's Hospital of Philadelphia, and the Merck Institute for Therapeutic Research, West Point, Pennsylvania, describes a measles serological survey conducted on normal children in an out-patient clinic and on mongolian idiots and other mental defectives in an institu-

tion both before and during a measles epidemic in the Philadelphia area.

Neutralizing antibodies were measured by determining the highest dilution of serum which would suppress the cytopathogenic effect of measles virus on human amnion cell cultures and complement-fixing antibodies were titrated against antigen prepared from human amnion cell culture. There was good correlation between the two types of serological antibodies. The complement fixation test was preferable for the serodiagnosis of measles because of its simplicity and because complement-fixing antibodies appear later in the infection than neutralizing antibodies. If a fourfold or greater rise in antibody titre was sought, then it was always evident with both types of antibody as long as the acute-phase specimen of serum was taken 3 weeks before the development of the rash. If the first specimen of serum was taken at the onset of the rash (as would be more likely in practice) then fourfold rises were noted in 93% of cases with the complement fixation test but only in 67% with the neutralization test. The neutralization test was efficient in distinguishing the immune subjects from those susceptible to measles.

Infants had usually lost all detectable maternal measles antibody by 6 months of age. In a low socio-economic group studied all children had acquired measles infection before 6 years of age. By contrast, some mentally retarded persons in the institution escaped infection until middle age. Evidence was presented that reinfection with natural measles may occur in an epidemic in persons with low levels of neutralizing antibody without causing clinically detectable illness.

D. Geraint James

257. Virological Diagnosis of Measles. [In English]

P. HALONEN, O. PETTAY, and I. SALMI. *Acta paediatrica* [Acta paediat. (Uppsala)] **51**, 27-32, Jan. [received March], 1962. 1 fig., 20 refs.

During an epidemic of measles in Helsinki in 1960 isolation of the virus was attempted in the Department of Virology of the University of Helsinki by inoculating throat washings from 25 patients and blood samples from 20 patients into human embryo kidney cultures, and into both primary cultures and a continuous line of human amnion cells.

No agents inducing giant-cell formation were isolated from any specimens, though viruses causing cytopathic effects like those of some enteroviruses were obtained from two throat swabs. The authors consider that their failure to isolate measles virus may be due to the type of cell culture used or to deficiencies in the tissue culture medium, and also to the fact that some specimens had been stored for several weeks at -60° C. before isolation was attempted. Serum obtained from all the patients showed a rise in the titre of complement-fixing antibody to measles from the acute to the convalescent phase of illness. No rise was observed in paired sera from children with other infectious diseases. The authors believe the diagnosis of measles by complement fixation tests to be of value since in one instance a child diagnosed as having German measles (rubella) developed complement-fixing antibodies, indicating that the disease was in fact measles, and in another instance a child who developed a rash after smallpox vaccination but was thought to have measles failed to develop complement-fixing antibodies to measles.

Janice Taverner

Pharmacology and Therapeutics

258. Studies of Delayed-action Medication. 1. Meprobamate Administered as Compressed Tablets and as Two Delayed-action Capsules

L. E. HOLLISTER. *New England Journal of Medicine* [New Engl. J. Med.] 266, 281-283, Feb. 8, 1962. 7 refs.

The author, working at the Veterans Administration Hospital and Stanford University School of Medicine, Palo Alto, California, has attempted to assess the value of administering a tranquillizer, meprobamate, in delayed-action form, the results obtained with two types of sustained-release capsules being compared with those of an ordinary compressed tablet. The three preparations and a placebo were given in random order to 16 healthy volunteers. Plasma levels and the urinary excretion of the drugs were measured and the subjective effects assessed. After 8 and 12 hours plasma levels were significantly higher when the delayed action capsules had been given. Urinary excretion in the first 4 hours was significantly higher after the tablets than after the capsules, but this was reversed during subsequent periods. Subjective symptoms were only slight and the author was unable to detect any striking difference between the effects of the four forms of treatment.

R. Schneider

259. Effect of Sorbitol on Iron Absorption in Man

A. LORÍA, L. SÁNCHEZ MEDAL, and J. ELIZONDO. *American Journal of Clinical Nutrition* [Amer. J. clin. Nutr.] 10, 124-127, Feb., 1962. 15 refs.

The authors, working at the Instituto Nacional de la Nutrición, Mexico City, have studied the effect of sorbitol on the absorption of iron. Nine normal adults and 3 patients with iron-deficiency anaemia were given 2 preparations of a solution of ferrous sulphate (6.66 mg. of iron per ml.), the second differing from the first only in that it contained 11.66 mg. of sorbitol per mg. of iron. The iron was labelled with 10 to 12 μ c. of $^{59}\text{FeSO}$ and the dosage was 0.5 mg. per kg. body weight. Each subject received each preparation at suitable intervals. Iron utilization for haemoglobin synthesis was calculated from the erythrocyte content of ^{59}Fe , 7, 10, and 14 days after the administration of the iron preparation.

Ten of the 12 subjects showed an increase in absorption when sorbitol was included in the iron preparation. The increase in absorption over that with iron alone varied from 35% to 137%, strongly suggesting that sorbitol can increase iron absorption in man.

A. E. Read

260. The Use of Polyglucin [Dextran] in the Treatment of Oedema. (Применение полиглюкина в лечении больных с отеками)

A. A. BAGDASAROV, P. M. AL'PERIN, V. E. KRUPJANKO, and T. V. POLUŠINA. *Клиническая Медицина* [Klin. Med. (Mosk.)] 40, 91-94, Jan., 1962.

The results of treatment of 18 patients with generalized oedema by the repeated drip infusion of 10% polyglucin (dextran) solution are here described. Four of the patients had cardiac oedema; in 7 others the cause was chronic

nephritis of the nephrotic type or amyloid nephrosis; in 5 it was hepatic cirrhosis with portal hypertension and ascites; and in 2 it was hyperproteinaemia due to nutritional deficiency and neoplastic cachexia respectively. The rate of infusion was 20 to 30 drops a minute, amounts of 150 to 250 ml. being given at intervals of 1 or 2 days and repeated up to a total of 13 infusions.

In the cases of cardiac oedema no durable benefit resulted and the patients were often more distressed at the end of treatment than before. In the patients with nephrosis the results were good. In those with cirrhosis little benefit was obtained. When the cedema was due to hypoproteinaemia the diuresis was satisfactory, but the patients required transfusions of plasma after the course of dextran infusions, which had not improved the level of blood protein. In no case was there any ill effect on renal function.

L. Firman-Edwards

261. Studies on a New Diuretic: Chlorothalidone

I. DYRDA, C. DUFAULT, J. G. HEBERT, G. TREMBLAY, and J. GENEST. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 475-482, March 17, 1962. 8 figs., 13 refs.

At the Hôtel-Dieu Hospital, Montreal, chlorthalidone, a recently synthesized diuretic, was given by mouth to a number of oedematous or hypertensive patients in dosages which varied, in different patients, from 50 mg. 3 times a week to 400 mg. a day. In all cases the drug resulted in marked diuresis and loss of weight. There was greatly increased excretion of potassium and sodium causing, when the larger doses were given, an excessive fall in the blood potassium level, necessitating administration of potassium by mouth. This fall produced orthostatic hypotension in some cases. Other side-effects included asthma, digestive disturbances, dizziness, and tachycardia, but it was rarely necessary to discontinue the drug. The authors point out that since the duration of action of chlorthalidone exceeds that of most other diuretic agents it need be given only 3 times a week for satisfactory results; it is 10 to 20 times as potent as chlorothiazide.

V. J. Woolley

262. The Use of Methyclothiazide ("Enduron") in Geriatric Patients

F. H. STERN. *Journal of the American Geriatrics Society* [J. Amer. Geriat. Soc.] 10, 256-258, March, 1962. 3 refs.

Methyclothiazide administered orally was a potent saluretic agent in the management of diverse types of edema and hypertension in a series of 25 geriatric patients. It was more effective than previously used diuretics such as organomercurial compounds given parenterally and thiazide derivatives. Methyclothiazide may be used safely with continued effectiveness in the treatment of moderate to severe edema. When used to initiate therapy, the drug also was of value in the treatment of mild to moderate hypertension. This antihypertensive action was insignificant, however, when the drug was used to augment the effects of rauwolfia derivatives in 3 patients with moderately severe or resistant hypertension.

The simplicity of administration and effectiveness of action are qualities which make methyclothiazide ideally suited for the management of edema and hypertension in geriatric patients.—[Author's summary.]

263. The Influence of Dosage on the Action of Modern Saluretics. (Der Einfluss der Dosierung auf die Wirkung moderner Saluretica)

K. FORMANEK and H. J. A. HÖLLER. *Wiener klinische Wochenschrift* [Wien. klin. Wschr.] 73, 702-703, Oct. 13, 1961. 2 figs., 5 refs.

The correlation between the dose of saluretics and the level of excretion of sodium, chloride, and potassium in the urine was investigated at the Institute for Experimental Pathology, Vienna, for the two diuretics hydrochlorothiazide and chlorthalidone; a group of 20 male albino rats being used for each dose. With both drugs sodium and chloride excretion reached a maximum with a dose of 1.25 mg. per kg. body weight. Excretion was then maintained at a lower level until a dose of 40 mg. per kg. was reached, when a precipitous fall in excretion occurred. Potassium excretion increased more gradually with both drugs, reaching its maximum with a dose of 5 mg. of hydrochlorothiazide per kg. and 40 mg. of chlorthalidone per kg.; larger doses again caused a precipitous fall in excretion. The authors suggest that an optimum dose also exists clinically, and that if this is exceeded not only does the excretion of sodium and chloride diminish, but that of potassium increases.

R. Schneider

264. A Comparison of the Gastrointestinal Absorption Rates of Plain and Buffered Acetylsalicylic Acid. [In English]

E. B. TRUITT JR. and A. M. MORGAN. *Archives internationales de pharmacodynamie et de therapie* [Arch. int. Pharmacodyn.] 135, 105-117, Jan. 1, 1962. 2 figs., 31 refs.

In a well-controlled cross-over trial, carried out on 30 healthy subjects at the University of Maryland School of Medicine, Baltimore, the effect of an antacid combination on the rate of absorption of aspirin was re-examined, the subjects receiving tablets of plain aspirin and tablets containing aspirin plus aluminium glycinate and magnesium carbonate. The tablets were commercially available and both products possessed similar disintegration times in water. The plasma salicylate level was determined at 10, 15, 20, and 30 minutes after the tablets were swallowed. Statistical analysis showed that the buffered tablet produced a plasma salicylate value approximately twice that produced by plain aspirin at each time period. It is pointed out that the ability to increase salicylate absorption is not a property common to all antacids. The possible mechanisms through which certain antacids accomplish this are reviewed.

W. C. Bowman

265. Subarachnoid Alcohol Block in the Control of Intractable Pain: Report of Results in 252 Patients

R. C. HAY. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 12-16, Jan.-Feb., 1962. 2 figs., 10 refs.

After a brief historical survey of the various methods which have been tried for the relief of intractable pain the author describes, from the Tumor Institute (University of Texas), Houston, his method of performing subarachnoid block with alcohol for this purpose. The patient is placed on the operating table with the affected side uppermost and

the table "broken" so that the painful segments are directly opposite the break. The patient is then rotated anteriorly through about 45 degrees and three lumbar puncture needles are inserted into adjacent intervertebral spaces. The patient must be warned that the injection may cause intense burning, warmth, or pain; however, this pain lasts only a few seconds and dies away in 2 to 3 minutes and its distribution indicates the accuracy of placement of the needles. The author considers it inadvisable to inject more than 1 ml. of absolute alcohol through each needle, and stresses that the patient's head and hips must be lower than the site of injection at all times. On completion the patient must then be kept immobile for 45 minutes, after which he is turned to the prone position and remains flat for a further hour.

The author has performed 407 such subarachnoid blocks in 252 patients, with "good" results (complete relief of pain) in 46%, "fair" results (that is, additional narcotic required) in 32%, and "poor" results in 14%. The average duration of relief was 3 to 4 months, and there were few serious complications.

Mark Swerdlow

266. The Effect of a Stimulant and a Depressant Drug on the Serial Rote Learning of Nonsense Syllables. [In English]

R. A. WILLETT. *Psychopharmacologia* [Psychopharmacologia (Berl.)] 3, 23-34, 1962. 2 figs., 25 refs.

It might be supposed that in the rote learning of nonsense syllables the performance of subjects receiving the stimulant drug amphetamine would be different from that of subjects receiving the depressant amylobarbitone (amytal), while subjects receiving placebos would react intermediately. In the investigation here reported from the Institute of Psychiatry, Maudsley Hospital, London, the performance of a group of subjects receiving 10 mg. of amphetamine was compared with that of groups receiving 4.5 grains [292 mg.] of sodium amytal and a placebo respectively. In the experiment, which was "double blind" and is described in detail, performance was measured on the serial rote learning of a list of 12 nonsense syllables. Various predictions were made about the expected results in the light of modern learning theory, but the actual results did not meet these predictions except in one respect, namely, that the subjects given amphetamine would show fewer behavioural oscillations. Various reasons for this finding are suggested and these are discussed in the light of present theories regarding conditioning and learning.

B. M. Davies

267. Unique Pharmacologic Properties of a New Non-barbiturate Anesthetic (G-29505). [In English]

J. C. BRINLING, T. D. SHOPIRO, and E. B. SIGG. *Archives internationales de pharmacodynamie et de therapie* [Arch. int. Pharmacodyn.] 136, 113-125, March 1, 1962. 6 figs., 9 refs.

G-29505, the diethylamide of 2-methoxy-4-allyl-phenoxy acetic acid, is an ultra-short-acting anesthetic which has been found to possess local anesthetic properties and to stimulate spinal reflexes and respiration. Evidence is presented that the reflex stimulation is central in nature and probably due to a direct effect on spinal motor neurons. Furthermore, the results suggest that the excitant effect on respiration is the result of three distinct actions of the drug, namely, stimulation of the carotid and aortic sinus mechanisms, of phrenic motor neurons in the spinal cord, and of the respiratory centers directly.—[Authors' summary.]

Chemotherapy

268. Studies on the Antibiotic Therapy of Serious Staphylococcal Infections. I. Comparison of the *in vitro* Activity of Methicillin, Phenethicillin, and Other Antibiotics

F. R. FEKETY JR. and L. E. CLUFF. *Annals of Internal Medicine* [Ann. Intern. Med.] 56, 198-206, Feb., 1962. 4 figs., 19 refs.

In this comparative study 100 strains of coagulase-positive staphylococci isolated at the Johns Hopkins Hospital, Baltimore, over the past 2 years were tested *in vitro* for their sensitivity to a number of antibiotics. It was found that methicillin was the most highly effective agent *in vitro*, only vancomycin among the other antibiotics tested showing a similar degree of effectiveness. The ease of administration of methicillin and the absence of side-effects give it a decided advantage over vancomycin in clinical practice. Benzylpenicillin, phenethicillin, tetracycline, and kanamycin are less useful because of the frequency with which strains become resistant to them; further kanamycin is also highly toxic. Nevertheless, if the causal organism is sensitive to benzylpenicillin the marked bactericidal action of this antibiotic, together with its ease of administration, lack of toxicity, and the low cost, make it the drug of choice. Chloramphenicol has excellent inhibitory properties, but it is a poor bactericidal agent and is potentially toxic; novobiocin and erythromycin occupy an intermediate position. Even though methicillin appears to be the mostly highly effective antibiotic the relative resistance to it of staphylococci of Phage-type 80/81 must be remembered and it may be that vancomycin is more efficacious for serious infections due to this type. The exact cause of the failure of methicillin to kill completely certain staphylococci has not been elucidated, but the authors believe that the results here reported suggest that it is related to the phenomenon of "drug indifference" described in detail by McDermott (*Yale J. Biol. Med.*, 1957-8, 30, 257). The bactericidal activity of methicillin varied widely; it was shown to be related to the size of the inoculum used in a sensitivity test and to vary with different strains of staphylococci.

The authors conclude that although benzylpenicillin is still the best antibiotic for sensitive staphylococci, methicillin or vancomycin should be used for the initial treatment of serious infections due to staphylococci whose sensitivity to antibiotics is not known.

R. F. Jennison

269. Treatment of Staphylococcal Infections with Methicillin

J. M. DICKINSON and N. B. PRIDE. *British Medical Journal* [Brit. med. J.] 1, 432-436, Feb. 17, 1962. 7 refs.

A trial of methicillin in the treatment of staphylococcal infection in 34 patients at Hammersmith Hospital, London, is reported. The dosage in adults was 6 g. daily for the first 48 hours and 4 g. daily thereafter by intramuscular injection, courses varying from a total of 24 g. to 136 g. Of 12 patients with respiratory infections (all with staphylococci resistant to at least penicillin and one other antibiotic) 6 with pneumonia and one with bronchitis responded satisfactorily. The remaining 5 either failed to respond or became in-

fectured again after an initial response; all 5 died, although death in 3 was primarily due to carcinoma of the lung. Methicillin was also given to 18 patients with non-respiratory staphylococcal infections, to 2 who were carriers of *Staphylococcus pyogenes*, and, prophylactically, to 2 patients who had undergone amputation of the leg. Summarizing the clinical results the authors state that the majority of patients receiving methicillin improved clinically, although in 12 the course was unfavourable. These 12 included, in addition to the 3 patients with bronchial carcinoma, a woman of 90 with cardiac failure and bronchitis, a patient with influenza who was moribund on admission, 2 patients with chronic infections in ischaemic limbs, 4 in whom the unfavourable course was not related to the infection, and one patient with a subphrenic abscess who responded initially but later had a relapse.

Staph. pyogenes was isolated from 24 of the 30 cases of clinical infection and *Staph. albus* from 2. In one case of pneumonia no sputum was obtained but *Staph. pyogenes* was isolated from the nose and in 3 cases infection with *Staph. pyogenes* was suspected but not proved. Methicillin was ineffective in removing the organism in 3 patients, while in a further 6 the organism was eliminated but reappeared after cessation of treatment. It was considered that in 4 of the latter group the staphylococcus was never fully eradicated and that in 2 cross-infection was probably responsible because the staphylococcus subsequently isolated was of a different phage type from that of the original strain. In 3 patients staphylococcus phage type 75/77+ was isolated which showed partial natural resistance to methicillin. The original staphylococcus was replaced by *Pseudomonas pyocyanea* in 8 cases. There were no side-effects or toxic reactions, but 2 thin patients complained that the injections were painful.

The authors conclude that methicillin is at present the antibiotic of choice in severe antibiotic-resistant staphylococcal infections. It is not suitable, however, for infections due to other organisms and should not be given in the treatment of patients with penicillin-sensitive staphylococcal infections.

P. T. Main

270. Treatment of Infectious Diseases in Children with Oral Phenethicillin

J. A. DUGGER. *Journal of New Drugs* [J. New Drugs] 1, 271-275, Nov.-Dec., 1961 [received April, 1962]. 12 refs.

A consecutive series of 200 children suffering from 306 penicillin-sensitive infections were treated [whether in hospital or at home is not stated] with phenethicillin by mouth. Their ages ranged from 1 month to 15 years. A liquid preparation ("alpen"; potassium α -phenoxethyl penicillin) was used for children up to 5 years in doses of 6 mg. per lb. (13.2 mg. per kg.) body weight daily. Tablets of 125 mg. (200,000 units) or 250 mg. (400,000 units) were used for children over 5 years old, the dosage (divided) at 5 to 8 years being 375 to 500 mg. daily; at 8 to 12 years 500 to 750 mg. daily; and at 12 to 15 years 1 g. daily. All tablets were given before meals or at bedtime.

Of the 306 infections, 87 were cases of purulent otitis media, 58 of bronchitis, 49 of pharyngitis, 39 of purulent tonsillitis, 15 of scarlet fever, 13 of cervical adenitis, 11 of impetigo, and the remainder miscellaneous. The majority of the patients in most groups were less than 5 years old.

The results were considered "excellent" in 122 cases and "good" in 161. [Criteria not given.] Eleven patients had supervening infection unresponsive to the oral penicillin and said to be due to penicillin insensitivity [technique not stated.] No gross toxic effects were seen.

I. M. Librach

271. Demethylchlortetracycline and Tetracycline Compared. Relative *in vitro* Activity and Comparative Serum Concentrations during 7 days of Continuous Therapy

W. M. SWEENEY, A. C. DORNBUSH, and S. M. HARDY. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 296-308, March, 1962. 1 fig., 11 refs.

The relative *in-vitro* activity against a group of micro-organisms and the comparative serum concentrations of demethylchlortetracycline (DMCT) and tetracycline (TC) hydrochlorides during 7 days of continuous therapy were studied at the Lederle Laboratories, Pearl River, New York. DMCT and TC were active against 97 out of 143 miscellaneous micro-organisms recently isolated from clinical sources. DMCT was about twice as active as TC in inhibiting the growth of the sensitive cultures.

The serum levels (measured microbiologically) produced by 3 different oral dosage schedules for DMCT and one oral dosage schedule for TC were compared in a cross-over study on 32 healthy subjects, dosage being continued over a 7-day period. During the 2nd to 7th days a 150-mg. dose of DMCT 4 times daily, with or without a loading dose, gave significantly higher serum levels (2.15 to 2.54 $\mu\text{g. per ml.}$) than a 250-mg. dose of TC 4 times daily (1.67 to 1.92 $\mu\text{g. per ml.}$). A dose of 300 mg. of DMCT twice daily gave similar serum levels (1.67 to 1.92 $\mu\text{g. per ml.}$) to 250 mg. of TC 4 times daily. During the treatment period 150-mg. doses of DMCT gave distinctly better results than 250-mg. doses of TC; it gave significantly higher concentrations of a more potent antibiotic. Significant amounts of DMCT (0.55 to 0.57 $\mu\text{g. per ml.}$) were present in the serum 60 hours after treatment had stopped, whereas the level of TC was then only 0.17 $\mu\text{g. per ml.}$

J. E. Page

272. Treatment of Dysentery and Gastroenteritis with a New Antibiotic, Polymyxin M. (Лечение дизентерии и колиэнтеритов новым антибиотиком полимиксином М)

N. V. GLADKOVA, A. D. SEMENOVA, and I. N. KRASNOVA. *Pediatriya* [Pediatriya] 40, 65-69, Feb., 1962.

A new Soviet antibiotic, polymyxin M, obtained from the culture-fluid of the spore-bearing soil organism *Bacillus polymyxa* Ross, is claimed to have high antibacterial activity against all Gram-negative bacteria (including *Escherichia coli*, *B. pyocyaneus*, *Salmonella*, *Brucella*, and the causal organisms of dysentery, typhoid and paratyphoid, cholera, and plague), the only exception being *B. proteus*. Gram-positive organisms are resistant to the drug and its use in staphylococcal enteritis is not recommended. The five other known polymyxins are briefly discussed; it is noted that only two (B and E) are of clinical use as A, C, and D are nephrotoxic.

The authors then report the results obtained with polymyxin M in 100 cases of gastro-intestinal infections in chil-

dren, including 80 cases of dysentery; 79% of the patients were under 2 years of age. In 72 of the cases of dysentery polymyxin M proved effective if given in a first course of at least 10 days (in some acute cases a second course was necessary 4 or 5 days later). There was no difference in the effect on various types of dysentery; Sonne, Flexner, and Newcastle strains were eliminated within 10 days in most cases. In 10 cases of staphylococcal enteritis polymyxin M was of no benefit. The dosage given was 10 mg. (100,000 units) per kg. body weight daily, in 4 separate doses. The content of a phial (500,000 units) was dissolved in 20 ml. of distilled water, giving a solution containing 25,000 units per ml. In this way each child received 1 ml. by mouth 4 times a day for each kg. of body weight.

L. Firman-Edwards

273. The Clinical Performance of Sulfamoxole, a New Sulfonamide: Analysis of 1240 Case Reports

P. F. CRAWFORD, K. R. CRAWLEY, and H. A. TUCKER. *Journal of New Drugs* [J. New Drugs] 1, 279-283, Nov.-Dec., 1961 [received April, 1962].

The experience of 46 independent clinicians who treated 1,240 patients during the first 6 months of 1961 with "sulfamoxole" ("sulfo"; "nuprin"; N-(4-5-dimethyl-2-oxazacyl) sulphanilamide) is reviewed by the Medical Division of the Upjohn Company, Kalamazoo, Michigan. Tablets of 500 mg. and 125 mg. were used. The daily dosage for children was 20 to 25 mg. per lb. (44 to 55 mg. per kg.) body weight in 12-hourly doses for 48 hours, after which it was halved; for adults 1 g. was given every 12 hours for 24 hours and 500 mg. 12-hourly thereafter. There were 582 male patients and 591 females and in 67 cases the sex was not stated. The patients' ages ranged from under 6 months to over 20 years.

There were 254 cases of ear, nose, and throat infection, 337 of respiratory infection, 314 of skin disease, 365 of urogenital infection, 52 of gastro-intestinal infection, and 79 of miscellaneous conditions. [Numerical incompatibilities occur throughout this paper—presumably owing to multiple injections and incomplete results.] Gram-positive organisms were responsible for 329 of the infections and Gram-negative organisms for 309. The results were "good" in 969 cases (69%) and "poor" in 262. Of 126 streptococcal infections, the results in 86 were "good"; of 149 staphylococcal infections, the results in 100 were "good". Of 309 Gram-negative infections, the results in 167 were "good", in 79 "poor", and 24 indeterminate. Of 33 cases of gonorrhoea, the results in 26 were "poor". Of 27 cases of *Shigella* infection, the results in 22 were "good". Of 87 infections with *Escherichia coli*, the results in 46 were "good" and in 23 "poor". Of 25 cases of *Proteus* infection, the results were "good" in 12. Toxic effects of the drug occurred on 73 occasions in 64 patients (5.2%). The commonest were nausea (20); skin rashes (15); intolerable taste (9); and depression (6). The drug had to be discontinued in 24 instances.

[The lack of adequate criteria of progress makes the results reported in this paper difficult to appraise. However, in the abstract's view, this new sulphonamide seems little different from its predecessors. Meningococcal meningitis is not mentioned, but it might be of value to try it in this condition.]

I. M. Librach

Infectious Diseases

274. A Case of Accidental Laboratory Infection with the Virus of Tick-borne Encephalitis. (Случай лабораторного заражения человека вирусом клещевого энцефалита) E. M. VIZEN and A. N. KNIAZEV. *Журнал Невропатологии и Психиатрии* [Zh. Neuropat. Psichiat.] 62, 333-338, No. 3, 1962. 6 figs.

The authors describe the case of a 44-year-old laboratory worker who accidentally pricked his finger with a syringe needle contaminated with the virus of tick-borne encephalitis. Prodromal symptoms of headache and general weakness appeared on the 15th day. To pronounced meningeal symptoms were later added signs of severe focal involvement of the central nervous system. The cerebrospinal fluid had a protein content of 1,320 mg. per 100 ml. and a pleocytosis of 1,408 cells per c.mm. consisting of lymphocytes and neutrophil granulocytes in approximately equal numbers. Investigation of the blood for the virus gave a positive result. Death supervened on the 23rd day.

Naked-eye examination of the brain showed meningeal inflammation and, on section, numerous haemorrhagic areas especially in the corpus striatum and visual cortex. Microscopical examination showed changes in the cortex, medulla, pons, and cervical cord. There were circumscribed areas of tissue disorganization. The nerve cells showed necrotic and degenerative changes. Plasma cells, lymphocytes, and monocytes lay sparsely, in clumps or round the vessels, and there was perivascular and pericellular oedema. The vessels showed stasis, thrombi, fibrinoid necrosis of their walls, and extravasations of blood. The authors point out that most of these pathological findings agree with those previously reported for infection acquired in the usual way, particularly with regard to the severe involvement of the medulla, cervical cord, and pons. They note, however, that the involvement of the visual cortex and corpus striatum together with the vascular and haemorrhagic components are in contrast to the usual picture in tick-borne encephalitis.

G. P. McGovern

275. An Epidemic of Aseptic Meningitis Syndrome Due to ECHO Virus Type 6. I. Correlation of Enterovirus Isolation with Illness

D. T. KARZON and A. L. BARRON. *Pediatrics* [Pediatrics] 29, 409-417, March, 1962. 22 refs.

An epidemic of aseptic meningitis occurred during the summer and autumn of 1955 in the western part of New York State. The authors now present a series of reports on the relationship of E.C.H.O. virus Type 6 to aseptic meningitis. This first paper contains a summary of the epidemic with the clinical-viral correlations and a description of cases of aseptic meningitis associated with other viruses. A total of 305 cases of disease involving the central nervous system and 40 of other illness were studied.

E.C.H.O. virus Type 6 was the predominant enterovirus associated with aseptic meningitis, as demonstrated by virus isolation and neutralizing antibody studies, being found in 85% of positive cases. Other types isolated were E.C.H.O. 14 (2.2%), E.C.H.O. 2 (1.4%), E.C.H.O. 18 (0.7%), Coxsackie virus (2.8%), unidentified viruses (4.3%), and polio

viruses (4.3%). There were no characteristic clinical features associated with these types. Aseptic meningitis is a syndrome of multiple aetiology. The stools were the best source of virus and showed a recovery rate of 74%. Cases of paralytic poliomyelitis were associated only with polio-virus infections and with Coxsackie or E.C.H.O. viruses.

John Fry

276. An Epidemic of Aseptic Meningitis Syndrome Due to ECHO Virus Type 6. II. A Clinical Study of ECHO 6 Infection

D. T. KARZON, N. S. HAYNER, W. WINKELSTEIN JR., and A. L. BARRON. *Pediatrics* [Pediatrics] 29, 418-431, March, 1962. 5 figs., 24 refs.

The second paper [see Abstract 275] describes the clinical features of 130 cases of aseptic meningitis associated with E.C.H.O. virus Type 6 infection. The onset was acute, with fever, muscle pains, headache, and vomiting, while pain in the chest was a feature in adults. Stiffness of the neck, back, and hamstrings was often noted. Mental involvement and disturbances of the cranial nerves did not occur. Peripheral reflexes were absent in 16% of the cases and mild transient muscle weakness occurred in 39%. The cerebrospinal fluid showed a pleocytosis and a raised protein content in 48% of the cases.

E.C.H.O. Type-6 virus was also isolated from contacts with presumed subclinical infections, from one girl with an encephalitis, and from a boy with the Guillain-Barré syndrome.

John Fry

277. An Epidemic of Aseptic Meningitis Syndrome Due to ECHO Virus Type 6. III. Sequelae Three Years after Infection

D. L. KING and D. T. KARZON. *Pediatrics* [Pediatrics] 29, 432-437, March, 1962. 9 refs.

This third paper [see Abstracts 275 and 276] reports the results in 93 patients who had suffered from aseptic meningitis due to E.C.H.O. virus Type 6 and who were followed up and re-examined 3 years after their acute infection to determine the extent of any residual disabilities. In addition, 9 other patients who had suffered from aseptic meningitis due to other enteroviruses and 19 patients with poliomyelitis were also examined, while 44 individuals with no previous history of disease of the central nervous system (C.N.S.) were studied for comparison.

Only minimal after-effects were noted in those patients who had suffered from aseptic meningitis. Approximately 20% of them gave a history of minor changes in behaviour and of tiredness, headaches, or muscle weakness. On examination, approximately 25% were found to have minor neurological signs such as altered reflexes, slight weakness of the neck or trunk muscles, or slight scoliosis. In contrast the patients who had had poliomyelitis showed severe and multiple changes. The control group with no history of C.N.S. disease also demonstrated an appreciable incidence of minor neuromuscular changes, thus further tending to minimize the significance of the findings in the patients who had suffered from aseptic meningitis.

John Fry

278. Behavior of Sabin Type I Attenuated Poliovirus in an Infant Population Infected with ECHO 14 Virus

V. G. INGRAM, M. L. LEPOW, R. J. WARREN, and F. C. ROBBINS. *Pediatrics* [Pediatrics] 29, 174-180, Feb., 1962. 3 figs., 15 refs.

This report from Western Reserve University School of Medicine, Ohio, describes the behaviour of two simultaneous infections, one (deliberate) with Sabin Type-1 attenuated poliovirus and one (natural) with E.C.H.O. virus Type 14, observed in an infants' home in Cleveland, Ohio. The average population in the home was 75 and the average duration of stay 6 months. During April and May, 1960, 25 babies, of whom 23 were aged between 10 and 16 weeks, and the other 2 were 5 and 8 months old respectively, were given orally 1 ml. of Sabin Type-1 attenuated poliovirus vaccine containing 10^6 TCID₅₀. Pre-immunization serological tests on these infants had shown 14 to have titres of 4 to 128 to poliovirus Type 1; in the others the titre was below 4, probably owing to residual maternal antibody or previous Salk vaccine immunization, which had been administered as a routine at the age of 2 months, but was discontinued from April, 1960.

Faecal and serological studies showed that all the 25 immunized children excreted poliovirus, 21 (84%) of them for longer than one week. Within one month 55% were serologically immune and 33% were classed as borderline since later sera for confirmation were not available. A study of the spread of the virus showed that 66% of the unvaccinated infants were infected with poliovirus and excreted it for 2 months. By October, 1960, the home was entirely free from this virus. During the immunization period and just after it, 45% of the entire population were found to be infected with E.C.H.O. virus, Type 14. Of the infants immunized against poliomyelitis 10 (40%) had been infected before and 5 after immunization. No clinical illness was attributed to E.C.H.O. 14 virus and only 12% of the population showed a significant rise in neutralizing antibodies. It appeared that in only 2 of the infants given the oral poliomyelitis vaccine was there any suggestion of interference with the immunization process. In conclusion the authors point out the limitations of this investigation for which, since it had not been planned, much of the information was perforce obtained only retrospectively.

[The real interest of the study lies in the complexity of problems presented by mixed infections with enteroviruses occurring while oral immunization is in progress.]

Kurt Schwarz

279. Clinical Findings and Vaccination Status in 98 Victims of Paralytic Poliomyelitis

M. ISHII and B. J. SPOULE. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 309-313, Feb. 17, 1962. 5 figs., 13 refs.

Throughout Canada 826 cases of paralytic poliomyelitis were reported during 1960, principally in the summer months, and in this paper the authors describe the clinical findings in 98 of these cases which were treated at the University of Alberta Hospital, Edmonton.

The greatest incidence (27.5%) was in the age group 5 to 9 years, but 29% of the patients were over the age of 20. Identification of the viral type was possible in 71 of the cases and proved to be Type 1 in 58 and Type 3 in the remaining 13. Examination of the cerebrospinal fluid in 69 cases

showed that there was an elevated cell count in 77.6% and an increased protein content in 68%, but chloride and glucose concentrations were within normal limits while blood cell counts were variable. Paralysis of the extremities and trunk, with or without involvement of the intercostal muscles, occurred in 65 cases, while there was bulbar involvement in 33 cases, in 8 of which it was of pure bulbar type. Respiratory difficulties occurred in 21 patients, but only 17 required respiratory assistance.

The mortality among the spinal cases was nil, but among the bulbar cases there were 7 deaths (an over-all mortality of 7.3%); only one of the patients who died was a female and 5 were over 20 years of age. Almost complete recovery was obtained in 35.7% of the patients, the proportion being greater in the bulbar group than in the spinal group, owing principally to the good recovery rate of 8 patients with isolated cranial nerve involvement. Just over 50% of the patients have been permanently crippled; a high percentage of these being aged 30 or more.

Full Salk vaccination had been received by 42 of the patients (42.8%), while 9 had been given partial vaccination. Comparison of the expected ratio to the actual ratio of vaccinated:non-vaccinated cases, if vaccination had been totally ineffective, showed that in the 0 to 4 age group the expected ratio was 9:1 but was actually 1.17:1; in the 5 to 19 age group the expected ratio was 3:1 compared with an actual ratio of 1.24:1; while in those 20 years old or more the ratios were: expected 0.33:1, actual 0.32:1. Thus it seems that vaccination had given protection against paralytic poliomyelitis. Of the patients who recovered 85.5% had had a full course of vaccine, whereas the proportion of completely vaccinated patients among those with severe residual effects was only 26%. Only one completely vaccinated individual died.

A. Ackroyd

280. Parainfluenza 2 (CA) Virus in Young Adults

W. J. MOGABGAB, E. C. DICK, and B. HOLMES. *American Journal of Hygiene* [Amer. J. Hyg.] 74, 304-310, Nov., 1961. 5 refs.

As part of a survey carried out at Tulane University School of Medicine, New Orleans, of the aetiology of respiratory tract infections in adults in Louisiana and Mississippi during 1958-9, evidence of parainfluenza-2 virus (croup-associated or CA virus) infection was sought by virus isolation in tissue culture and by serological evidence of haemagglutination-inhibition. Primary monkey kidney cultures were found to be more sensitive than HeLa cells for virus isolation, and virus was recovered from more than half the cases that subsequently showed increases in the haemagglutination-inhibition antibody titre. If a fourfold or greater increase in circulating antibodies was considered to reflect recent infection, then there was serological evidence of parainfluenza-2 respiratory tract disease in 1.7% of 1,061 cases studied. They were mild infections with malaise, sore throat, cough, and hoarseness.

D. Geraint James

281. Adjuvant Influenza Adenovirus Vaccine

G. MEIKLEJOHN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 594-597, Feb. 24, 1962. 5 figs., 13 refs.

During the winter of 1959-60, a controlled field trial was conducted at a U.S. military base in Denver, Colorado, to assess the value of a polyvalent influenza and adenovirus

vaccine consisting of 8 antigens emulsified in a mineral oil-aralcel base. The antigen, comprising 4 influenza-A strains, 2 influenza-B strains, and 2 adenovirus strains, was injected into the triceps of 2,303 men while a control group of 2,256 men received a 1:1,000 solution of formalin-saline. Sera obtained 6 weeks after vaccination revealed satisfactory haemagglutination-inhibition antibody titres for various influenza strains, particularly A2 (Japan 305), A1 (AA57), and B1 (GL55). In adenovirus neutralization tests, four-fold or greater increases in Type-7 antibody titres were noted in half the sera tested. Comparable results were not observed in neutralization tests with Type 4. Increases in adenovirus complement-fixing antibodies were infrequent.

The control and vaccinated groups differed sharply in their responses during the following 3 months when a winter epidemic of respiratory disease occurred. Thus the incidence of influenza was 17 times greater and that of adenovirus infection 10 times greater in the control than in the vaccinated group. In patients with no rise in antibody for influenza or adenovirus—a crucial control—there was no difference in the incidence of other respiratory diseases as between the vaccinated and control groups.

D. Geraint James

282. Inactivated Measles Virus Vaccine. II. Prevention of Natural and Experimental Measles with the Vaccine

H. A. FELDMAN, A. NOVACK, and J. WARREN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 391-397, Feb. 10, 1962. 8 refs.

In this study either an alum-containing, concentrated, formalin-inactivated measles virus vaccine or a placebo (alum alone) was administered intramuscularly at monthly intervals to alternate children (63 subjects) belonging to 22 families in Syracuse, New York. The unexpected occurrence of an epidemic of measles interrupted the immunization programme of 3 doses, each of 0.5 ml., at monthly intervals. Of the 18 subjects who received all 3 doses 13 (72%) showed serological conversion, compared with 53% of those receiving 2 doses and 4% of those receiving only one dose of the vaccine. The acquisition of any level of antibody resulted in solid immunity to "wild" virus challenge, whereas all those in the placebo-treated group and exposed to measles became severely ill. Modification of the disease in this group occurred only in the 3 who had received gamma globulin. On subsequent challenge with live attenuated measles virus vaccine the immunized children remained well, even if their antibodies were no longer detectable, while the placebo group had some symptoms; both had excellent serological responses. It is stated that this inactivated measles virus vaccine is safe, simple to administer, and effective in affording protection against natural and experimental measles.

D. Geraint James

283. Inactivated Measles Virus Vaccine. III. A Field Trial in Young School Children

W. WINKELSTEIN JR., R. JENSS, G. E. GRESHAM, D. T. KARZON, and W. E. MOSHER. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 398-403, Feb. 10, 1962. 2 figs., 4 refs.

A double-blind trial of the inactivated measles virus vaccine described above [see Abstract 282] was carried out during 1961 in 15 schools in Buffalo, New York, 330 children receiving the vaccine and 319 the placebo, the former in

3 doses of 0.5 ml. each intramuscularly. The first 2 injections were one week apart and the third was 4 weeks after the first. The vaccine produced a good neutralizing antibody response, prevented measles, and reduced the school absentee rate in the course of 3 months' study.

D. Geraint James

284. Hemorrhagic Phenomena in Infectious Mononucleosis

H. R. SHUMACHER and S. J. BARCLAY. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 175-182, Feb., 1962. 26 refs.

In this paper the authors analyse 497 cases of infectious mononucleosis seen at the U.S. Naval Hospital, Portsmouth, Virginia, between January, 1955, and March, 1960, with special reference to the serious complication of haemorrhagic phenomena. In 45 cases the diagnostic criteria were not acceptable, but of the 452 remaining cases (415 in males) 31 (6.9%) showed haemorrhagic manifestations, in the form of oronasopharyngeal bleeding in 10 cases, petechiae or ecchymoses in 16, haematuria in 5, gastro-intestinal bleeding in 3, and rupture of the spleen in one case; some patients suffered more than one form. A fairly extensive review of the literature of these haemorrhagic complications showed that splenic rupture has been the one most commonly associated with a fatal outcome. It may occur following palpation of the spleen or be produced by the most trivial strain.

A. W. H. Foxell

285. Cardiovascular Damage in Leptospiral Diseases. (О поражении сердечно-сосудистой системы при лептоспирозных заболеваниях)

JA. S. PUPKEVIČ-DIAMANT. *Клиническая Медицина* [Klin. Med. (Mosk.)] 40, 84-90, Jan., 1962. 28 refs.

An investigation of 753 patients with leptospiral infections revealed cardiac and vascular injury in a large proportion of cases. Of the 753 cases, 119 were identified as being due to *Leptospira grippo-typhosa*, 617 to *L. pomona*, 6 to *L. canicola*, and 11 to *L. icterohaemorrhagiae*, 705 being in men and 48 women. Cardiac abnormalities were found in 56.3% of the first group and 68.4% of the second. The incidence was higher in older patients and in those more severely ill. Of 89 patients examined electrocardiographically, 80 showed abnormal changes, although 30 of these had no clinical signs of cardiac damage. Out of 32 of these patients who were examined after convalescence, the changes had disappeared in 4, had improved in 10, and worsened in 9. The abnormalities varied from splintering and widening of the P wave to extrasystoles and delay in atrio-ventricular conduction. Myocarditis developed on the 6th day in one case and on the 52nd day in another. Some patients developed auricular flutter and others fibrillation.

Of 63 patients examined personally by the author, all were found to have increased capillary permeability. Of the patients with *L. pomona* infection, 23.5% had various types of rash, 6.4% epistaxis, 2.9% scleral haemorrhages, and 1.2% haematuria. In the group infected with *L. grippo-typhosa* the percentage incidence of haemorrhages was higher. Of 136 patients with leptospirosis whose arterial blood pressure was studied dynamically, in 59.7% both systolic and diastolic pressures were reduced, whereas in 26.3% the diastolic pressure alone was reduced. The fall was greatest between the 15th and 20th days of illness and

coincided with the fall of temperature. Abnormal pulse rates were common, the most frequent finding being bradycardia. There are ample grounds from the present data for regarding the cardiovascular system as being particularly vulnerable to leptospiral infection. *L. Firman-Edwards*

BACTERIAL DISEASES

286. **Studies of the Epidemiology of Staphylococcal Infection. IV. The Changing Ecology of Hospital Staphylococci** L. S. COHEN, F. R. FEKETTY, and L. E. CLUFF. *New England Journal of Medicine* [New Engl. J. Med.] 266, 367-372, Feb. 22, 1962. 5 figs., 37 refs.

A bacteriological study of staphylococcal infections acquired by patients in the Johns Hopkins Hospital, Baltimore, during 1959 showed that *Staphylococcus aureus* Phage-type 80/81 was the single commonest organism isolated, 32% of the infections being due to this type, while 41% were due to a variety of strains other than 80/81. However, from September, 1959, a decrease in the number of infections due to Type 80/81 was noted and this persisted until May, 1961; during that period this type accounted for only 10.6% of hospital infections and the decrease was associated with an increase in the number of infections due to strains not typable by the routine test dilution (R.T.D.) of bacteriophage. However, when these staphylococci were typed with R.T.D. $\times 1,000$ a number of them were found to be of Type 54, which now accounted for 24% of the hospital infections, whereas previously it had rarely been responsible.

Infections among hospital staff were usually due to Type 80/81 and a further survey showed that no member of the staff had had an infection due to Type 54. Examination of nasal swabs from 100 members of the staff showed that whereas 5 carried staphylococci of Type 80/81 only one carried those of Type 54. Nose swabs from patients were also examined and it was shown that Type 54 was now the single most common staphylococcus present in the nose of patients. It is suggested that the change in the distribution of strains of staphylococcus in the Hospital may be related to the progressively increased use of neomycin for sterilization of the bowel before operation. Type 54 is particularly resistant to neomycin and kanamycin, whereas most strains of Type 80/81 are sensitive. It is noted that although this change in the epidemiological pattern of staphylococcal infection appeared to be related to the greater use of neomycin there was no over-all increase in the number of infections due to staphylococci in the Hospital.

R. F. Jennison

287. **Bacteremia Due to Gram-negative Bacilli: Review of 113 Cases Encountered in the Five-year Period 1955 through 1959**

M. C. MCHENRY, W. J. MARTIN, and W. E. WELLMAN. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 207-219, Feb., 1962. 36 refs.

There have been several reports in the literature of a recent increase in the incidence of infections due to Gram-negative bacilli. During the 5-year period from 1955 to 1959 the authors have observed at the Mayo Clinic 113 such cases occurring in 74 males and 39 females. Although the patients' ages ranged from 9 days to 91 years, 60% of them were aged 60 years or more. Thus the infection appears to

occur predominantly among middle-aged or older male patients with an acquired abnormality of the urinary tract. In 62 cases (55%) the portal of entry was the genito-urinary tract; in 40 the infection followed an operation, instrumentation, or radiation. Of the other 51 cases the portal of entry was the gastro-intestinal tract in 21, the skin in 3, the respiratory tract in 2, and in one a postoperatively infected arterial graft; in the remaining 24 cases the cause or route of infection was not evident. The most commonly found Gram-negative bacilli belonged to the coli-aerogenes group; *Pseudomonas* was the cause of the bacteraemia in 19 patients. For the treatment of *Pseudomonas* infections the authors found polymyxin B an effective agent, while for infections due to Gram-negative bacilli of enteric origin streptomycin and tetracycline were the most useful.

Franz Heimann

288. **Septicaemia Due to Gram-negative Bacilli**

C. H. TALBOT. *Lancet* [Lancet] 1, 668-670, March 31, 1962. 14 refs.

The author presents from the Royal Infirmary, Bristol, a review of 20 cases of septicaemia due to Gram-negative bacilli, of which 2 were fatal. Of these 20 patients 12 presented the classic signs and symptoms of septicaemia, but the remaining 8 suffered from "bacteraemic shock" with a very low systolic blood pressure. Hypotension was usually associated with infection by *Proteus* species; thus of 9 patients with *Proteus* infections 6 became hypotensive, compared with only 2 of 8 cases of septicaemia due to coliform organisms. No hypotension developed in 3 cases of infection due to *Pseudomonas*. The author points out the importance of early antibiotic treatment, especially in cases showing bacteraemic shock. Tests for sensitivity of the various strains of Gram-negative bacilli isolated revealed that kanamycin was the only antibiotic to which all the *Proteus* strains were sensitive. Coliform bacilli responded well both to chloramphenicol and kanamycin. For the treatment of infections due to *Ps. pyocyanea* the author recommends polymyxin.

Franz Heimann

289. **Intramuscular Meprobamate in the Treatment of Tetanus in Infants and Children**

F. H. HOWARD and W. DEVERE. *Journal of Pediatrics* [J. Pediat.] 60, 421-429, March, 1962. 29 refs.

The authors of this paper from Dhahran Health Center, Dhahran, Saudi Arabia, describe the results obtained with meprobamate in controlling spasms in 10 infants and 5 older children suffering from tetanus. The drug was administered by intramuscular injection in an 8% solution in polyethylene glycol, the initial dosage in neonates being 80 to 100 mg. every 3 hours. In addition to the meprobamate the children were given tetanus antitoxin, phenobarbitone, and some were also given chlorpromazine. A group of 26 comparable patients who did not receive meprobamate served for purposes of comparison. There was no difference between the mortality in the treated group and that in the control group, but in the former the spasms lasted for a shorter time and the relaxation between the spasms was more complete. The duration of stay in hospital was also shorter in the meprobamate-treated group. The authors emphasize that while meprobamate is partially effective in controlling the spasms "the search for a more effective anticonvulsant drug must continue".

Winston Turner

Tuberculosis

290. **The Evolution of Primary Tuberculous Infections in the Past Twenty Years.** (L'évolution des primo-infections tuberculeuses depuis vingt ans)

P. FRÉOUR, J. GERMOUTY, and P. ROGER. *Revue de la tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 25, 1227-1234, Nov., 1961 [received Feb., 1962].

The authors present a study of 422 cases of primary tuberculosis in children occurring between 1943 and 1959 and compare the results in 207 cases treated before 1951 when isoniazid was first introduced and 215 cases treated after that date. The primary infection appeared to be clinically less grave in the latter group. The rate of healing of the disease was no greater in the later group than in the earlier, at the end of 6 months 73.5% of the first group being cured compared with 51.8% of the second group. The miliary and infiltrative lesions recovered more rapidly with isoniazid, but forms with lymph-node involvement, present in most of the cases, were little influenced. On the other hand, isoniazid presented the onset of complications and there was only one death in the group treated after 1951 compared with 15 in the group treated before that date.

G. M. Little

291. **Percutaneous Multiple Puncture Inoculation of Freeze-dried BCG**

W. J. BELL. *British Journal of Diseases of the Chest* [Brit. J. Dis. Chest] 56, 11-16, Jan., 1962. 2 figs., 20 refs.

In this investigation, carried out under the auspices of the West African Council for Medical Research, Ghana, a comparison was made of the tuberculin sensitivity in some 1,500 school-children after B.C.G. vaccination either by intracutaneous injection or by multiple puncture. Those vaccinated by the intracutaneous method received 0.1 ml. of freeze dried vaccine (100,000 viable organisms), while those vaccinated by multiple puncture were divided into three groups which were vaccinated respectively with an apparatus containing either 6 needles, or one with 18 needles, or received two vaccinations at different sites with the latter. The multiple puncture needles were set to penetrate 2 mm. in all cases and the vaccine contained 50 to 75 mg. weight of organisms per ml.

Post-vaccination Heaf tests showed a conversion rate of 91.3% in the group given intracutaneous vaccination, whereas the rates for the multiple puncture groups were: 6 needles 51.3%, 18 needles 57.9%, and 36 needles 72.5%. Moreover, the positive reactions in the intracutaneous group were greater in degree than in the multiple puncture group. It is concluded that B.C.G. vaccination by multiple puncture requires further development before its routine use can be recommended.

T. M. Pollock

292. **Serum Proteins in Pulmonary Tuberculosis**

J. A. PILHÉU, J. A. IANNELLO, R. BONACOSSA TORRENT, and J. A. WILLSON. *Diseases of the Chest* [Dis. Chest] 41, 173-179, Feb., 1962. 4 figs., 14 refs.

At the University Tuberculosis Clinic, Buenos Aires, the serum protein pattern was studied by means of paper electrophoresis in 107 tuberculous patients and in 12 healthy

individuals who served as a control group. It was found that in direct proportion to the gravity of the tuberculous condition there was a decrease in the serum albumin fraction, but the total serum proteins showed no change. In the increase in the globulin fraction which occurs in severe disease the γ -globulin value was always highest. In the most severe cases the α_2 -globulin fraction also tended to increase, the albumin:globulin ratio decreasing in direct proportion to the severity of the lesion.

It is suggested that study of the serum protein fractions is useful in determining the degree of activity of a tuberculous lesion and also for observing and assessing the progress of the disease.

Kenneth M. A. Perry

293. **Vaccine Treatment of Chronic Pulmonary Tuberculosis with B.C.G.** (La vaccinoterapia con B.C.G. nella tubercolosi cronica polmonare)

R. ITALIA, G. POZZI, and S. SCOCCIA. *Notiziario dell'Istituto vaccinogeno antituberculare* [Notiz. Ist. vaccin. anti-tuberc.] 11, 329-362, Oct.-Dec., 1961 [received Feb., 1962]. Bibliography.

The authors have added B.C.G. vaccine to the chemotherapeutic regimen in 26 patients with chronic pulmonary tuberculosis who were being treated at the Guido Salvini Sanatorium, Milan. One month after a test dose of 100 μ g., doses of B.C.G. were given by mouth monthly to a total of 550 to 650 μ g. In 5 patients there was radiological and clinical deterioration, in 3 no change, in 13 minor radiological and clinical improvement was observed, and in 5 the cavities closed and the sputum became negative. The B.C.G. was well tolerated and there were no vaccinal reactions, even in the patients whose condition deteriorated. In half of the patients tuberculin sensitivity was increased, sometimes fivefold, and was unchanged in the remainder. The authors conclude that any beneficial effect observed in these patients was due to an allergic stimulation of indolent chronic tuberculous lesions and that the exudative forms produced are then more amenable to the action of chemotherapeutic agents.

Arnold Pines

294. **The Prognosis of Pulmonary Tuberculous Cavities Treated with Antibiotics (250 Cases).** (Le devenir des cavernes tuberculeuses pulmonaires traitées par les antibiotiques (250 observations))

C. MATTEI, P. LAVAL, P. BALOZET, A. BARBE, and Y. BAILLE. *Revue de la tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 25, 1187-1199, Nov., 1961 [received Feb., 1962]. 4 figs., 22 refs.

The authors report a 3- to 6-month follow-up study of 171 male and 79 female patients with pulmonary tuberculous cavities who were treated with antituberculous drugs, of which at least two were given simultaneously in all cases and in some cases three, while 28 patients received corticosteroids in addition. The sputum became negative in 80% of the series, but the results of treatment depended on the age of the patient. Thus, of those aged 16 to 20 years 95% showed very good results, in the age group 20 to 30 years the figure was 65.5%, while of patients aged 60 to 70

years only 14% showed very good results. In 78 cases artificial pneumothorax was induced in conjunction with antibiotic treatment. The authors found this a most efficacious weapon against persistent cavity lesions, the antituberculous drugs preventing the onset of pleural complication and allowing the pneumothorax to be abandoned after 2 years.

G. M. Little

295. Pulmonary Tuberculosis as a Cause of Respiratory Insufficiency (Classification and Anatomico-clinical Basis). (Les tuberculoses pulmonaires génératrices d'insuffisance respiratoire (classification et bases anatomo-cliniques))

J. BRUN, J. C. KALB, M. PERRIN-FAYOLLE, H. POZZETTO, J. GARDÈRE, G. CASSAN. *Revue de la tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 25, 1200-1226, Nov., 1961 [received Feb., 1962]. 7 figs, 3 refs.

A study based on 82 patients (69 men and 13 women) who developed respiratory insufficiency as a direct result of pulmonary tuberculosis is described. This insufficiency was rare if the tuberculosis was cured in 3 years or less; it was most common in subjects between 40 and 60 years of age. There was also a high percentage of patients defaulting from treatment. Radiologically those cases showing some collapse were most common (43%), compared with 30% in which there were ulcero-caseous lesions alone.

The authors discuss the type of respiratory defects seen and consider that they are due to factors affecting the lung tissue, bronchi, pleura, and diaphragm and favouring emphysema. They consider that in some cases prolonged courses of antibiotics may increase the respiratory insufficiency owing to their fibrosing effect, and in certain cases these drugs may have to be withdrawn.

G. M. Little

296. The Effect of Adrenocortical and Androgenic Steroid Supplements in Tuberculous Patients Receiving Chemotherapy S. COHEN, M. GROSS, R. GROSSMAN, and G. KLAUITTER. *Diseases of the Chest* [Dis. Chest] 41, 150-160, Feb., 1962. 3 figs.

In an attempt to evaluate the effect of giving corticosteroids in conjunction with antituberculous chemotherapy three groups of patients at the B. S. Pollak Hospital for Chest Diseases, New Jersey, were observed. Group A included 10 patients with active pulmonary tuberculosis, in 7 far advanced and in 3 moderately advanced, who had not been treated with chemotherapy previously; their ages ranged from 17 to 51 years, all had cavitation, and 9 had a positive sputum. Group B consisted of 10 similar patients with far advanced active pulmonary tuberculosis whose ages ranged between 31 and 64. Group C consisted of 97 patients with comparable disease who had been observed over a period of 2 years. Group A received prednisolone, 15 mg. 3 times a day for 3 days, then 10 mg. 3 times a day for 3 days, and finally 5 mg. 3 times daily for 12 weeks. Group B were given testosterone but not prednisolone, and Group C received neither of these drugs.

Little difference in the results of treatment in the three groups was observed, patients in Group C given chemotherapy alone progressed as satisfactorily as those in the other two groups. However, in Group A about half the patients showed some gain in weight which was greater than that in the other two groups. The authors consider, however, that this response can often be achieved in such patients with an anabolic steroid preparation alone without

resorting to the more hazardous use of adrenocortical steroids and they feel that the routine initial use of adrenocortical agents in conjunction with chemotherapy for previously untreated active pulmonary tuberculosis appears to be unnecessary and may lead to unexpected side-effects.

Kenneth M. A. Perry

297. Results of Repeated Antibiotic Treatment in Relapses of Pulmonary Tuberculosis. (Résultats du traitement antibiotique itératif dans les rechutes de la tuberculose pulmonaire)

J. VIDAL, J. J. GUIN, and Y. DECOR. *Revue de la tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 25, 1405-1414, Dec., 1961 [received April, 1962].

This paper reports the results obtained with antibiotic antituberculous drugs in the treatment of 50 cases of pulmonary tuberculosis in relapse, of which 26 had previously been treated by the authors and 24 elsewhere. In all cases strict criteria for the acceptance of a cure of the first attack were applied, 6 months follow-up without sign of activity being considered the minimum. The relapse was treated with intravenous PAS, 15 g. daily, isoniazid in a daily dose of 5 to 10 mg. per kg. body weight, and streptomycin, 1 g. on alternate days.

Among the 47 patients who completed the course a cure was obtained in 8 out of 10 women, but in only 23 out of 37 men. An analysis of the anatomical distribution of the lesion during the first attack showed that the least good results were obtained in those cases in which there had been some fibrosis. Patients who had developed a cavity during the first attack which had healed responded well during the relapse.

On analysing the results in relation to treatment previously given it was noted that by far the best cure rate (89%) was in those cases in which treatment of the original disease had not been unduly prolonged. The over-all cure rate of the relapse was 66%.

H. F. Reichenfeld

298. Tuberculous Mediastinal Adenopathy in the Adult Developing at a Long Interval after the Primary Infection. (Les adénopathies médiastinales tuberculeuses de l'adulte se développant en dehors de la primo-infection)

H. BROCARD and R. VANNIER. *Poumon et le cœur* [Poumon] 18, 107-127, 1962. 44 refs.

That young adults suffering from primary tuberculous infection may develop mediastinal adenopathies has long been established, but the occurrence of such an adenopathy in a tuberculin-positive adult at some considerable time after the primary infection is less well known, though the earliest reports cited by the authors go back to 1914. These adenopathies, because of their resemblance to tumour masses, have been named mediastinal tuberculomas. They then describe a number of interesting cases which help to illustrate the circumstances in which these problems are encountered; these include (1) satellite adenopathies of pulmonary tuberculosis; (2) adenopathies developing in spite of successful chemotherapy for parenchymal tuberculosis; and (3) isolated adenopathies. This last type is the most important; and several illustrative cases are presented to emphasize the difficulty of differentiation of this lesion from reticulosis, neoplasm, and sarcoidosis. Thoracotomy is recommended both as a diagnostic and as a therapeutic measure.

A. J. Karlish

Venereal Diseases

299. Incidence of General Paralysis of the Insane

S. M. LAIRD. *British Medical Journal* [Brit. med. J.] 1, 524-526, Feb. 24, 1962. 7 refs.

The investigation herein described was designed to determine whether there has been an increase in the incidence of general paralysis of the insane (G.P.I.) which might be a sequel to the wartime increase in early syphilis and the difficulties of treatment at that time. Although there have been reports recently of significant numbers of new cases of G.P.I., the author found that between 1950 and 1961 in the Manchester area there was a decrease in the number of cases diagnosed. In 1960 the number of cases of G.P.I. diagnosed (51) was smaller than in any previous year of the decade.

[This survey is significant because it presents an analysis of the trend of this disease over a decade and the population studied numbered over 4,000,000.]

Robert Lees

300. Syphilis: Review of the Recent Literature, 1960-1961

H. BEERMAN, L. NICHOLAS, I. L. SCHAMBERG, and M. S. GREENBERG. *Archives of Internal Medicine* [Arch. intern. Med.] 109, 323-344, March, 1962. Bibliography.

301. The Significance of the Nelson Test in Paediatrics.

(Die Bedeutung des Nelson-Tests für die Kinderheilkunde) J. MEYER-ROHN. *Archiv für Kinderheilkunde* [Arch. Kinderheilk.] 165, 259-269, Feb., 1962. 22 refs.

Of the three treponemal antibodies recognized in the past 15 years, namely, the Pangborn phospholipid-cardiolipin reagin, the treponemal specific antigen, and the treponemal immobilizing protein of Nelson, the last-named has been shown to be present only in true cases of syphilis (except for pinta and frambosia).

Since immobilisin appears only late in the secondary stage of syphilis, the usual dark-field examinations and standard serological tests are of more use than the treponemal immobilization (T.P.I.) test in early cases, but the latter comes into its own in the consideration of latent syphilis, where it can be used to eliminate the numerous false positive results obtained with the more regularly employed Wassermann and complement fixation tests. Similarly in the tertiary stage of syphilis occasionally encountered in the long-standing tabetic in whom both serum and spinal fluid tests are negative, the T.P.I. test is almost always positive in the untreated case. In all these forms of acquired syphilis it may be assumed that the reversion of an originally positive T.P.I. reaction to a negative one indicates cure of the infection.

At the University Skin Clinic, Hamburg-Eppendorf, experience with the test in suspected congenital syphilis underlines the fact that, since approximately one year is required for the full development of immobilisin, the presence of an initially positive test does not necessarily identify an infected infant, nor does a negative result rule out congenital syphilis. It is possible that there is a transplacental passage of immobilisin. Obviously the standard serological tests cannot safely be ignored, but the T.P.I. test serves a useful

purpose in establishing the true diagnosis in the face of equivocal results from other investigations.

Allene Scott

302. A New "One-minute" Treatment of Gonorrhoea

A. SIBOULET and P. DUREL. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 37, 240-243, Dec., 1961 [received Feb., 1962]. 15 refs.

In this paper from the Institut Fournier and Hôpital Saint-Louis, Paris, trials are reported of a new "one-minute" treatment of acute gonococcal urethritis in which a single dose of 2.5 g. of the oral antibiotic spiramycin was taken by the patient in the presence of a doctor. These trials were considered necessary because of the growing failure rate with streptomycin, the risk of hypersensitivity reactions to penicillin, and the unsatisfactory results of oral treatment of out-patients when the drug is taken away from the hospital. In 784 males and 58 females gonococcal urethritis was diagnosed on examination of methylene-blue or Gram-stained smears, the diagnosis being confirmed by culture in all the females but only in those males in whom there was doubt at the first examination. As soon as the diagnosis was established the patient took 10 tablets (2.5 g.) of spiramycin with 2 glasses of water in the presence of the doctor, the name of the drug not being disclosed.

Tests of cure included a provocative test in which 1% silver nitrate was instilled into the urethra after 48 hours, 3 days, and 7 days. Serological tests were carried out 3 weeks and 3 months after treatment. Similarly, provocative tests were repeated in the follow-up of females, and although few patients of either sex were followed up for long, these tests made it likely that relapses could not be overlooked. The cure rate was 97.4% in the males and 98.1% in the females.

After a series of clinical trials of sensitivity of 61 strains, a serum level of spiramycin of 1 µg. per ml. maintained for 5 to 6 hours was thought to ensure cure of gonococcal urethritis, all strains examined being sensitive to the antibiotic at this level. Tolerance of the drug was excellent and there were no side-effects.

A. J. Gill

303. Preliminary Observations on the Treatment of Gonorrhoea with Kanamycin Sulphate by Intramuscular Injection

B. PIGUET. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 37, 244-246, Dec., 1961 [received Feb., 1962]. 6 refs.

Experience with kanamycin in the treatment of gonorrhoea is described in this paper from the Institut Fournier, Paris. The antibiotic was given intramuscularly in three dosage schedules to 48 males with gonorrhoea as follows: a single injection of 1 g. only (7 patients), 1 g. daily for 2 days (25 patients), and 1 g. daily for 3 days (16 patients). Of the 7 patients given 1 g. only, 3 were cured and 3 others responded to further kanamycin. There were no failures in the group given 1 g. daily for 2 days, but of the 16 given a 3-day course (3 g.) one did not respond. Kanamycin was also successful in 3 females with gonococcal leucorrhoea. No toxic manifestations were reported.

A. J. Gill

Tropical Medicine

304. Serum Vitamin B₁₂ and Folic Acid (P.G.A.) Levels in Hypoproteinaemia and Marasmus in Indian Children

R. S. SATOSKAR, B. S. KULKARNI, B. M. MEHTA, R. R. SANZGIRI, and M. S. BAMJI. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 9-16, Feb., 1962. 4 figs., 29 refs.

The serum protein pattern and the serum vitamin B₁₂ (cyanocobalamin) and folic acid levels were studied in Indian children suffering from protein malnutrition and marasmus. High serum vitamin B₁₂ levels have been reported in various forms of liver disease as well as in some cases of protein malnutrition. Base line values were established in three groups of Indian children—40 healthy newborn infants weighing over 5 lb. (2.26 kg.) at birth, 17 healthy children aged 3 to 10 years, and 10 children aged 4 to 10 years with respiratory infection. Serum total proteins averaged 6.58 g. per 100 ml. in normal children with 4.02 g. albumin and 2.55 g. globulin per 100 ml. Gamma-globulin ranged from 1.2 g. per 100 ml. in infants through 1.33 g. in normal children to 1.9 g. per 100 ml. in children with respiratory infection. Serum folic acid levels averaged 69.4 μg . per ml. in infants; 13.9 μg . in healthy children, and 18.9 μg . in those with respiratory infection.

In a group of 28 cases of malnutrition (20 of protein malnutrition and 8 of marasmus) there were clinical signs of multiple deficiencies of vitamins and minerals as well as of proteins. Some degree of anaemia was present in 24 cases. The blood picture was monocytic in 11, microcytic in 13, and macrocytic in only 4 cases. The serum protein level was low in all cases, mainly at the expense of the albumin factor. In nearly two-thirds of the patients the gamma-globulin level was high, as compared with a value of 1.33 g. per 100 ml. in healthy children. The highest values were noted in cases of respiratory or intestinal infection; the gamma-globulin level was over 2.75 g. per 100 ml. in 3 patients with cirrhotic changes in the liver. Liver biopsy, which was performed in all cases, showed that the pathological changes varied from swelling of parenchymatous cells to cirrhosis in fatty liver. The serum vitamin B₁₂ level ranged from 60 to 6,500 μg . per ml.; it was over 1,000 μg . per ml. in 16 of the cases. The high figures could not be correlated with the clinical severity of the disease; with changes in total globulin values, or with any factor linked with the total leucocyte count, but were related to the severity of the fatty changes in the liver. Serum folic acid levels showed wide variations from 3 μg . to 100 μg . per ml., the significance of which was not clear. A study of convalescents showed that in 4 cases of hypoproteinaemia and 2 of marasmus the vitamin B₁₂ levels fell to normal as the patients recovered.

William Hughes

305. Intramuscular Amopyroquin for Acute Malaria

M. T. HOEKENGA. *American Journal of Tropical Medicine and Hygiene* [Amer. J. trop. Med. Hyg.] 11, 1-5, Jan. [received March], 1962. 1 fig., 8 refs.

Amopyroquin ("propoquin"; 7-chloro-4-[4-hydroxy-3-1'-pyrrolidinyl-methylphenyl]aminoquinoline dihydrochloride), which is closely related to amodiaquin, was given as a

single intramuscular injection to 525 Panamanian patients with acute malaria; since the patients came from a district in which transmission of the disease occurs throughout the year most of them were partially immune. The dose used initially was 150 mg. of amopyroquin base (later reduced to 90 mg. with equally good results) in a volume of 5 ml. for adults and older children; smaller children were given "correspondingly less". [Older children are designated as over 10 years in the text and younger children as under 12 years of age in the table of results. Further, all the results are analysed together as a single group.]

For the 282 cases of *Plasmodium falciparum* malaria the average time taken for the temperature to return to normal was 22.4 hours, while for the 243 cases of *P. vivax* infection this time was 15.5 hours; parasites of both species disappeared from the blood in a mean time of 31.4 hours. Figures previously determined in a comparable series of patients showed that an intramuscular dose of chloroquine caused defervescence in 29.8 hours (*P. falciparum*) and 21.1 hours (*P. vivax*), and parasites disappeared in 34.1 and 34.2 hours respectively, while in patients treated with hydroxy-chloroquine defervescence occurred in 21.7 hours (*P. falciparum*) and parasites disappeared in 33 hours. The author states that the favourable results of amopyroquin treatment are apparent [but no figures are given for the variance of the means and it is not possible to judge whether or not the differences are significant]. With amopyroquin 6 of the 282 patients with *P. falciparum* malaria and 4 of the 243 with *P. vivax* infection did not respond satisfactorily. The corresponding figures for chloroquine were 10 out of 210 with *P. falciparum* and 3 of 90 with *P. vivax* malaria. No toxic side-effects of amopyroquin were observed. There were some complaints of pain at the site of injection immediately after the dose was given, but this was no more severe than that observed with sodium or potassium penicillin. No local tissue reaction was subsequently observed in any patient.

The author recommends intramuscular injection of amopyroquin for patients with acute malaria who require parenteral medication.

L. G. Goodwin

306. Entamide and Furamide in the Treatment of Amoebic Infection in Nakuru, Kenya

L. B. NEVILL. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [Trans. roy. Soc. trop. Med. Hyg.] 56, 81-84, Jan., 1962. 14 refs.

Amoebiasis is common in the Nakuru district of Kenya, and during 1959 a total of 127 patients with this disease were treated at the provincial hospital. Diagnosis was microscopical and symptoms varied from acute to chronic dysentery. Almost all the patients took part in trials of amoebicides, and the present paper describes the results obtained with "entamide" (diloxamide) and its furoate salt "furamide". Entamide was given to 22 patients, adults receiving 2 to 4 g. daily for 7 days and children 20 mg. per kg. daily for 7 days. Stools were free from amoebae by the 3rd day of treatment, and 21 patients were negative for

Entamoeba histolytica on their discharge from hospital. Of 7 patients re-examined one month after discharge, all gave a negative result. No side-effects were observed. Furamide was given to 18 patients, adults receiving 2 to 3 g. daily for 7 days and children between 0.75 and 1.25 g. daily for 7 days. On the 6th day of treatment one patient developed albuminuria, which cleared up after 4 days. All 18 patients were free from *E. histolytica* on discharge. A few patients were followed up, and all remained negative.

R. A. Neal

307. Bone Changes in Leprosy. Their Incidence, Progress, Prevention and Arrest

D. E. PATERSON. *International Journal of Leprosy [Int. J. Leprosy]* 29, 393-422, Oct.-Dec., 1961 [received April, 1962]. 12 figs., 17 refs.

The author presents a study of bone changes in leprosy which is based on the radiographic findings in 108 patients examined at the Christian Medical College, Vellore, S. India, and 894 patients in the Hay Ling Chau leprosarium, Hong Kong. Serial follow-up radiographs over 1 to 3 years were studied in 144 cases during treatment.

The bone findings could be classified under three main headings—specific, non-specific, and osteoporosis. Specific changes were closely studied first in the fingers of 8 patients receiving treatment all of whom showed destruction of bone underneath local lesions of lepra reaction. In these cases healing with almost complete restitution of the normal bone contours was observed following treatment with DDS. From these observations it was considered that 128 (14.3%) of the 894 patients in Hong Kong showed signs of specific changes due to osteitis leprosa; of these patients only 3.0% had active lesions. The radiographic appearances included honeycombing, pseudocyst formation, enlarged nutrient foramina, subarticular collapse, and multiple small clear-cut areas of bone destruction, this last being the most definite sign of an active lesion. Healing may occur either with or without sclerosis and deformity. It is noted that these specific changes are for all practical purposes seen almost only in the bones of the hands and feet.

In 45% of cases non-specific changes were observed. These included osteitis and osteomyelitis similar to those in other conditions. Concentric absorption as seen in subacute and chronic neurotrophic osteitis was found in 14% of cases and is well illustrated in the author's radiographs, in which various degrees of absorption of phalanges and metatarsals are seen. The metacarpals are rarely involved. Aseptic necrosis may result in absorption of the tufts of the phalanges. All the radiographic signs of acute, subacute, and chronic arthritis were noted. In the wrist, subluxation may occur following arthritis. In the tarsus, infection may spread from ulceration of the heel to the os calcis and thence to other tarsal bones, leading to complete destruction of these bones. Charcot-type joint destruction was also observed. In the skull there may be absorption of the nasal spine of the maxilla, pre-maxilla, and alveolar margins. It is remarked that such changes have been found in ancient skeletons excavated in Europe. Osteoporosis was present in 10% of the Hong Kong cases. From serial radiographs taken during treatment the affected bone could be seen to return to normal density in some cases. Angiographic studies showed diminution in size of the vascular end-loops of the digital arteries where there was soft tissue absorption or osteoporosis. The incidence of osteoporosis and non-

specific bone changes increases with age. There is also a close correlation between occupation and non-specific changes other than osteoporosis. In some 80 to 90% of patients with anaesthesia of hands or feet in whom infection and ulceration occur there is evidence of bone damage. The author advocates immobilization of joints to prevent deformity during treatment. The paper is illustrated with excellent photographs of the various bone changes described.

William Hughes

308. The Food of *Glossina palpalis* (R-D) and its Bearing on the Control of Sleeping Sickness in Forest Country

K. R. S. MORRIS. *Journal of Tropical Medicine and Hygiene [J. trop. Med. Hyg.]* 65, 12-23, Jan., 1962. 4 figs., 26 refs.

The control of the tsetse fly *Glossina palpalis* is particularly difficult in forest and broken forest areas. The present investigation was carried out in the extreme north of Liberia during 1959-60 where sleeping sickness was endemic in 1940-44, the vector being *G. palpalis* subspecies *gambiense*. The sparse population (30 per sq. mile (12 per sq. km.)) had reduced the original forest to a mosaic of farms and secondary forest. Tsetse density was low and often it was difficult to catch even 2 or 3 flies per day, and these only in places such as bridges or fords where people drew water or washed clothes. The forest land contained ample choice of mammals and reptiles, but in the inhabited areas man seemed to be the main source of food for *G. palpalis*. Sampling by means of fly traps was carried out along the Zeliba river at 5 sites differing in degrees of human contact, 4 traps being set at each site.

The results of observations made over 18 weeks of the wet season, July to November, 1959, were as follows: 215 flies were caught in the area where human contacts were numerous, 85 where they were less numerous, 21 where they were only occasional, 14 where rare, and only one fly where there were no human contacts. Similar observations made over 10 weeks at the same trapping sites during the dry season, January to March, 1960, when contacts along the river were more frequent, gave comparable results, in each case there being a direct correlation between the catch and the amount of human contact.

Trapping was also undertaken along the Lawa river in uninhabited primary forest where an abundant *G. palpalis* community was found to be subsisting on wild game and crocodiles. Sand-digging operations on this river were started close to 2 of the traps and the disturbance was followed by a reduction in the number of flies caught. Thereafter the larger vertebrates were virtually eliminated by hunting and this resulted in a further reduction to a density similar to that on the Zeliba river. The author then found that reductions of 70 to 80% or more in the incidence of *G. palpalis* could be effected in 4 to 8 weeks by trapping at the main points of man-fly contact such as bridges, fords, and water-holes. It was further shown that trapping all the points of man-fly contact along 1½ miles (2.5 km.) of river lying close to a town could almost certainly eliminate all *G. palpalis* from that stretch of river. The experiments demonstrate the value of trapping as a means of controlling trypanosomiasis in man under the difficult conditions of broken forest country. It is considered that the efficacy of the "Morris" type of trap used in this study could be greatly increased by its treatment with insecticides and attractant scents.

Edward Hindle

Nutrition and Metabolism

309. One Year of Sodium Dextrothyroxine Therapy for Hypercholesterolemia

B. M. COHEN. *Angiology* [Angiology] 13, 69-74, Feb., 1962. 36 refs.

The author of this paper from Saint Elizabeth and the General Hospitals, Elizabeth, New Jersey, observed for over one year a group of 30 ambulatory hypercholesteremic patients (serum cholesterol level well over 250 mg. per 100 ml.) who were receiving sodium D-thyroxine treatment. Of the 30 patients 6 were considered to have idiopathic hypercholesteremia, 6 had not received any treatment for spontaneous hypothyroidism, and 18 were under treatment for cardiovascular disease, including 8 who had had previous myocardial infarction with subsequent angina pectoris. Among the 18 patients in the last group were 6 diabetics and 5 patients who had been receiving continuous anticoagulant therapy for 8 months to 2 years. The daily dose of sodium D-thyroxine ranged from 4 to 8 mg.

The mean pre-treatment serum cholesterol level of 351.9 mg. per 100 ml. was reduced after a year by 32.3%. During the first 20 weeks of therapy the reduction was highest in patients showing the highest pre-treatment level, but the reduction became surprisingly homogeneous in all patients after 52 weeks. The serum protein-bound iodine level rose in all patients during treatment, the average pretreatment level of 5.16 μ g. rising at the end of one year to 12.21 μ g. per 100 ml.

Tremor, increased perspiration, and insomnia were not observed, nor could other signs of hypermetabolism be detected in spite of the conspicuous increase in the serum protein-bound iodine concentration. Only one of the 8 patients with the anginal syndrome experienced a transient increase in precordial distress, which responded to a reduction in the dosage of the drug. Of the remaining 7 patients 3 became completely free from anginal symptoms after 20 weeks and 4 others experienced less angina (effort tolerance improved and nitroglycerin requirements became less). No truly toxic effects were observed in this series.

Z. A. Leitner

310. Objective Effects of Dextrothyroxine Therapy

W. R. OWEN, J. C. OWENS, and W. B. NEELY. *Angiology* [Angiology] 13, 75-78, Feb., 1962. 8 refs.

The objective effects are reported of D-thyroxine in a daily dosage of 4 to 8 mg. in 70 patients seen at Hermann Hospital, Houston, Texas. On the average a 25% reduction in the serum cholesterol level was achieved after 3 months' treatment. If the cholesterol level was not reduced below 260 mg. per 100 ml. 0.5 g. of nicotinic acid 3 times daily was added to the treatment regimen and this helped further to reduce the level. When the drug was withdrawn the serum cholesterol level rose again.

Radioactive-carbon studies in animals have revealed an increased faecal excretion of cholesterol after administration of D-thyroxine. In a patient with an external biliary fistula on a stable fat intake there was a 200% increase in cholesterol excretion after 10 days' treatment with D-thyroxine. In several members of a family suffering from

essential hypercholesterolemia the size of xanthomata diminished substantially with the reduction in the serum cholesterol level following D-thyroxine treatment.

Symptoms of angina pectoris were improved in most patients. In 14 receiving warfarin a prolongation of the prothrombin time with a reduction in the prothrombin concentration was observed. In these patients liver function was not impaired, as judged by excretion of "bromsulphalein" and by the serum glutamic-oxalacetic transaminase level; thus the potentiation of warfarin was not effected by reduced liver function.

Z. A. Leitner

311. Cholesterol Reduction in Patients with Arteriosclerosis

A. BERNSTEIN and F. SIMON. *Angiology* [Angiology] 13, 79-80, Feb., 1962. 3 refs.

The authors of this paper from Beth Israel Hospital, Newark, New Jersey, describe the effects of D-thyroxine in 23 patients (20 male and 3 female, aged 45 to 62 years) suffering from coronary artery disease. The drug was given in a dosage of 2 or 4 mg. daily, and the patients were observed for 5 to 6 months. Over this period the serum cholesterol level was reduced on the average by 15%. Transitory side-effects such as heartburn and nervousness were observed occasionally but they did not interfere with further treatment.

Z. A. Leitner

312. The Effect of Dextrothyroxine on the Disappearance from the Blood of C¹⁴-Labelled Cholesterol: a Preliminary Report

J. L. RABINOWITZ, T. RODMAN, and T. L. SMOLINSKY. *Angiology* [Angiology] 13, 81-84, Feb., 1962. 4 figs., 3 refs.

The effect of orally administered D-thyroxine on the catabolism of serum cholesterol was studied at the Veterans Administration Hospital, Philadelphia. For this purpose 1 to 3 mg. of cholesterol labelled with radioactive carbon was dissolved in 0.3 ml. of ethanol, the solution being added to 10 ml. of sterile blood. Immediately after preparation this suspension of cholesterol in blood was injected very slowly (10 to 15 minutes) intravenously. The patients selected for study did not receive D-thyroxine for 30 days after the radioactive cholesterol had been given. The peak level of serum radioactivity was achieved in 3 to 4 days after administration. Before D-thyroxine was given it took 8 to 10 days for the serum radioactivity to fall to 50% of the peak level, but after administration of the drug a fall to the 50% level occurred by the 4th day in all patients. Only a small amount of radioactive CO₂ was detected in the expired air of patients, with a peak at the 6th to 7th days. After D-thyroxine "a several-fold increase" in radioactive CO₂ with a peak at the 3rd to 4th days was observed.

The serum cholesterol level was stable during the baseline period but began to fall when the patients received D-thyroxine in a dosage of 8 mg. daily. After 25 days of D-thyroxine therapy the serum cholesterol level was still falling. The maximum observed reduction was 66% and the minimum 34%. A small calorogenic effect was observed in 2 patients. It is suggested that D-thyroxine markedly accelerates the breakdown of body cholesterol.

Z. A. Leitner

313. The Use of Triparanol and Sodium Dextrothyroxine to Lower Serum Cholesterol

E. M. GOYETTE and A. SAAD. *Angiology* [Angiology] 13, 89-93, Feb., 1962. 1 ref.

An investigation of the comparative efficacy of triparanol and D-thyroxine in lowering the serum cholesterol level is reported from Huron Road Hospital, Cleveland, Ohio. A group of 121 patients were given an average daily dose of 250 mg. of triparanol for 7 months. In 102 patients the serum cholesterol level was reduced, the mean fall being 19.1%. In the remaining 19 patients there was a rise in the level, amounting to 14%. About 10% of the patients had unpleasant side-effects (gastro-intestinal disturbances, giant urticaria, loss of hair, and impotence). In 84 out of 116 patients given 4 mg. of D-thyroxine daily the serum cholesterol level fell, the mean reduction being 19.3% (very similar to that with triparanol). Side-effects were less numerous in this group, but 5 patients thought that angina became worse during the treatment. A combination of both drugs in patients who failed to respond to either alone, reduced the pre-treatment serum cholesterol level by about 17%. No evidence was found that a reduction in the serum cholesterol level had any beneficial effect on the ischaemic heart disease of the patients. Z. A. Leitner

314. Thyroid Analogs as Cholesteropenic Agents

H. R. HOFF, R. J. SPERBER, S. FISCH, and A. C. DEGRAFF. *Angiology* [Angiology] 13, 94-99, Feb., 1962. 2 figs., 36 refs.

At the Veterans Administration Hospital, Bronx, New York, the effect of D-triiodothyronine on the serum cholesterol level was evaluated in a double-blind trial. In all the 4 patients participating the serum cholesterol level was adequately reduced. In 3, however, the basal metabolic rate (B.M.R.) rose during a treatment period of 14 weeks by about 30%; the remaining patient who had previously had myocardial infarction sustained another infarction after 6 weeks on the drug. The trial of this drug was therefore discontinued.

Sodium D-thyroxine was given to 13 hypercholesterolaemic patients, including 5 with coronary heart disease. The trial was carried out over two periods of 6 weeks each. In the initial 6-week period the serum cholesterol level was reduced in all patients whether they received a placebo or D-thyroxine. Substitution of D-thyroxine for the placebo for 6 weeks did not reduce the level further, but substitution of the placebo in the group initially receiving D-thyroxine resulted in a statistically significant rise in serum cholesterol level.

The serum protein-bound iodine level rose in all patients given D-thyroxine. In one of the 5 patients with coronary artery disease angina was aggravated during administration of 4 mg. of D-thyroxine daily and improved during treatment with a placebo. Another patient with previous myocardial infarction had a further acute infarction at the end of treatment, while the B.M.R., pulse rate, and body weight remained substantially unchanged.

The authors state that their findings "suggest a trend, but do not establish definitely the efficacy of D-thyroxine".

[The findings in this paper and the 5 papers abstracted above (see Abstracts 309-313) confirm previous knowledge that D-thyroxine significantly lowers the serum cholesterol level. Although the calorogenic activity of the drug appears to be the lowest among the so far known thyroid analogues, D-thyroxine substantially raises the serum protein-bound

iodine level and increases anginal symptoms in some of the patients suffering from coronary artery disease. See also *Abstr. Wld Med.*, 1961, 30, 211.] Z. A. Leitner

315. Cause of Hypoalbuminaemia in Patients with Gastro-intestinal and Cardiac Disease

K. N. JEEJEEBHAY. *Lancet* [Lancet] 1, 343-348, Feb. 17, 1962. 2 figs., 22 refs.

Gastro-intestinal protein loss and albumin turnover have been studied at the West Middlesex Hospital, Isleworth, by the technique of injecting tracer amounts of radioiodinated human serum albumin and trapping the albumin secreted into the intestine by means of "amberlite" ion-exchange resin, as described by Jeejeebhoy and Coghill (*Gut*, 1961, 2, 123; *Abstr. Wld Med.*, 1961, 30, 453). The 35 patients investigated included 8 without alimentary disease who served as controls, 25 patients with gastro-intestinal disorders 10 of whom had normal serum albumin levels and 15 had hypoalbuminaemia (serum albumin level less than 3.5 mg. per 100 ml.), 2 of these having undergone intestinal resection, and finally 2 patients with cardiac disease and hypoalbuminaemia. The serum albumin and the total exchangeable albumin (T.E.A.) levels were determined in all cases; the latter is the vascular and extravascular body albumin in which the tracer is distributed. The albumin turnover, also determined, comprises the exogenous turnover in the gut and endogenous turnover within the body.

In the controls the serum albumin level ranged from 3.5 to 4.2 g. per 100 ml., the T.E.A. from 3.8 to 5.0 g. per kg. body weight, the mean albumin turnover was 218 mg. per kg. per day, and the faecal excretion of albumin from 1.1 to 3.8 g. per day. The exogenous turnover in these normal controls was 28 to 62 mg. per kg. per day, and the endogenous turnover, derived by subtraction, was 100 to 242 mg. per kg. per day.

In the patients with gastro-intestinal disease but no hypoalbuminaemia, the results were mostly within the normal range. In those with gastro-intestinal disease and hypoalbuminaemia it was shown that of 12 of these with a low T.E.A. value 7 also had a low endogenous turnover. There was a high degree of correlation ($r=0.9$) between endogenous albumin turnover and T.E.A. In those patients with hypoalbuminaemia the synthesis of albumin was insufficient to maintain normal endogenous turnover in the presence of appreciable gastro-intestinal loss. In 4 patients who were treated with human serum albumin (25 g. on alternate days up to a total of 200 g.) it was found that despite continued faecal loss of albumin the endogenous turnover had increased; 3 of the patients maintained their serum albumin levels for 3 to 5 months. Exogenous turnover is thought to occur mainly in the jejunum. Both gastro-intestinal protein loss and endogenous turnover were increased in patients with cardiac disease.

The author suggests that patients with hypoalbuminaemia can be divided into three groups: (1) those with excessive loss of albumin into the gut and in whom albumin synthesis cannot maintain the endogenous turnover of the protein; (2) patients with no gastro-intestinal loss of protein in whom synthetic activity is subnormal; and (3) those in whom hypoalbuminaemia is apparently due to an uneven distribution of albumin between the vascular and extravascular compartments. The cause of the variation in synthetic activity is not understood. J. S. Malpas

Gastroenterology

316. An Evaluation of a Long-acting Anticholinergic-antacid in the Treatment of Peptic Ulcer and Other Diseases of the Digestive Tract

H. C. MOELLER and J. A. RIDER. *American Journal of Gastroenterology* [Amer. J. Gastroent.] 37, 73-78, Jan., 1962.

Since there is a delay between the ingestion of any anticholinergic drug and the onset of its action, it was thought that the prescription of a long-acting anticholinergic together with an antacid might be useful in the treatment of peptic ulcer. The basic gastric acidity (maximum free hydrochloric acid) and the urinary excretion of uropepsin were determined in 20 patients with peptic ulcer at the University of California Medical Center, San Francisco. The prescribed tablet ("bepHan spacetabs") contained: 0.5 mg. of total laevorotatory alkaloids of belladonna, 450 mg. of aluminium hydroxide-glycine, and 60 mg. of magnesium oxide. The patients received the treatment for a period of 4 to 12 months [the number of tablets prescribed daily is not stated]. The basic gastric acidity and the urinary uropepsin were again determined at the end of treatment. It was found that the basic gastric acidity was lower in 17 patients by an average of 27%, and the urinary excretion of uropepsin had decreased in 16 by an average of 24%.

The clinical response to the preparation was then observed in 103 patients (48 men and 55 women), aged from 18 to 78 years, suffering from various gastro-intestinal conditions, namely, duodenal ulcer in 38 cases, gastric ulcer in 4, the post-gastrectomy syndrome in 8, gastritis in 9, and functional bowel distress in 44. Treatment lasted for periods varying from 6 to 18 months. The results were assessed as good or excellent in 73 cases (71%), this number including 28 of the 38 patients with duodenal ulcer and 3 of the 4 with gastric ulcer. The incidence of undesirable side-effects was very low (approximately 8%). The prescribed preparation produced a sustained anticholinergic and antisecretory effect in patients with peptic ulcer. It is considered that this combination of drugs is of value in the medical treatment of peptic ulcer and other gastro-intestinal conditions.

Joseph Parness

317. Protein Tolerance in Liver Disease

C. M. LEEVY, WOO YOON CHEY, P. A. ARTS, C. L. MENDENHALL, and M. M. HOWARD. *American Journal of Clinical Nutrition* [Amer. J. clin. Nutr.] 10, 46-55, Jan., 1962. 18 refs.

The effects of ingesting a standard meal containing 60 g. of protein on the blood concentration of ammonia were investigated at Jersey City Medical Center, New Jersey, in 15 normal subjects, 40 patients with hepatic cirrhosis, and 6 with viral hepatitis. No patient had evidence of gastro-intestinal haemorrhage. Needle biopsy of the liver and biochemical tests were carried out on every patient.

The fasting ammonia concentration in normal subjects ranged from 20 to 60 μ g. per 100 ml., and no significant changes occurred after ingesting glucose, meat protein, or milk protein. There was also no increase in the blood ammonia level in patients with mild or moderate cirrhosis, but in those with severe cirrhosis both meat and milk pro-

duced a large increase in this level and frequently precipitated lethargy, disorientation, or coma. The increase in the blood ammonia concentration after the test meal was related to the fasting arterial ammonia level and to the results of various liver function tests. With fasting values of greater than 100 μ g. per 100 ml. there was always an abnormal ammonia tolerance. In normal subjects the fasting hepatic venous ammonia level was slightly higher than the arterial level, but after the test meal the position was reversed. In 3 patients with (presumed) arterio-venous shunts, and in active liver-cell necrosis the meal caused a greater rise in ammonia levels in hepatic venous blood than in arterial blood. In 3 patients with a portacaval shunt and 2 with intrahepatic collaterals [query misprint for extrahepatic collaterals?] the rise in ammonia level was greater in arterial than in hepatic venous blood.

Studies *in vitro* indicated that protein digestion is important in producing abnormally high blood ammonia levels. Administration of antibiotics, lactobacillus therapy, or infusion of arginine or glutamate reduced the fasting blood ammonia concentration but not the response to a test meal. Restriction of protein is therefore necessary in patients with severe cirrhosis.

W. H. Horner Andrews

318. Levels of Glutamine and Ammonia and the pH of Cerebrospinal Fluid and Plasma in Patients with Liver Disease

J. CAESAR. *Clinical Science* [Clin. Sci.] 22, 33-41, Feb., 1962. 5 figs., 31 refs.

Because of the known fact that in severe hepatic disease there is derangement of the metabolism of ammonia which in turn may be associated with changes in neurological function, the author has determined, at the Royal Free Hospital, London, the pH and the levels of glutamine, ammonia, protein, and bilirubin in the cerebrospinal fluid (C.S.F.) and plasma of patients with liver disease. From 35 patients with cirrhosis of the liver blood samples were withdrawn for examination of plasma while in 18 of them the C.S.F. was also similarly investigated, the findings being compared with those in 10 control subjects without liver disease, in 5 of whom the C.S.F. was examined.

The mean concentration of glutamine (which is responsible for the transport of free ammonia) in the plasma of the control subjects was 9.9 ± 2.3 mg. per 100 ml. while in the patients with liver disease it was very similar, namely, 11.9 ± 3.2 mg. per 100 ml. In contrast, the glutamine concentration in the cerebrospinal fluid of the patients with liver disease was significantly increased, the mean value being 26.4 ± 14.8 mg. per 100 ml., compared with the normal value of 10.5 ± 2.9 mg. per 100 ml.; 5 of the 6 patients with neurological changes showed especially high values. The mean plasma ammonia level in the 10 control subjects was 0.78μ g. per ml. (S.D. 0.12), whereas in three-quarters of the patients with liver disease, including 5 with neurological changes, the concentration of ammonia was raised, the mean value for all the hepatic patients being 1.28μ g. per ml. (S.D. 0.69), an increase which is statistically significant. Ammonia concentrations in the cerebrospinal fluid were

much lower in the control subjects than in the patients. The relationships between concentration of various other substances were also studied. There was a poor correlation between the C.S.F. and plasma concentrations of ammonia. However, the mean ammonia content ratio C.S.F.: plasma was significantly higher in the hepatic patients, confirming that in liver disease the C.S.F. concentration is more consistently elevated than that of the plasma. There was a significant correlation between ammonia and glutamine concentrations in the C.S.F., but there was no relationship between the levels of these substances and the serum albumin, bilirubin, and transaminase levels or the presence of ascites. There were no constant changes in pH in either the plasma or C.S.F. in the patients studied. The equilibrium ratio of the distribution of radioactive bromide in the C.S.F. and plasma was within normal limits in 17 of the 18 patients in whom it was determined.

W. H. Horner Andrews

319. Experience with the Ammonium Chloride Tolerance Test in Portal Hypertension with Special Reference to Its Use as a Function Test after Portacaval Anastomosis. (Klinische Erfahrungen mit der Ammoniumchloridbelastung beim Pfortaderhochdruck, insbesondere als Funktionstest portokavalärer Anastomosen)

G. HENNRICH. *Acta hepato-splenologica* [*Acta hepato-splenol. (Stuttg.)*] 9, 1-16, Feb., 1962. 5 figs., 49 refs.

The author reports from the University Surgical Clinic, Bonn-Venusberg, the results of an ammonium tolerance test carried out in 7 patients with cirrhosis of the liver but no evident portal hypertension, 28 with cirrhosis of the liver and portal hypertension, and in 29 with cirrhosis of the liver after, or in some cases before and after, portacaval or splenorenal anastomosis. (The test was apparently carried out on only 4 control subjects without liver disease.) The patients were given 3 g. of ammonium chloride by mouth every 40 minutes for up to 200 minutes and serial estimations of venous blood ammonia were made over the same period. A significant rise in blood ammonia levels in patients after portacaval anastomosis suggested that the shunt was still patent and this appeared to be the main value of the test. In unoperated patients with cirrhosis of the liver a positive test was thought to indicate the existence of a collateral circulation, but the results were too variable for this to be of value in the early diagnosis of portal hypertension.

P. C. Reynell

320. Immediate and Prolonged Therapeutic Effects of Corticotrophin and Adrenal Steroids in Ulcerative Colitis: Observations in 340 Cases for Periods up to Ten Years

J. A. SPENCER, J. B. KIRSNER, P. MLYNÁRYK, P. I. REED, and W. L. PALMER. *Gastroenterology* [*Gastroenterology*] 42, 113-129, Feb., 1962. 12 refs.

The authors report, from the University of Chicago, a study of the long-term therapeutic effects of steroids and corticotrophin (ACTH) in 170 male and 170 female patients with ulcerative colitis, the follow-up period being not less than one year and in many cases over 10 years.

The immediate effect of steroid or ACTH therapy was good in 58% and moderately good in 22% of the patients; as might be expected, most of the failures occurred in patients who were severely ill. Those with moderately severe disease fared a little better than those with severe or mild disease. The sustained response to prolonged treatment (more than

2 months) was good in 43% and moderately good in 30% of the patients; the authors state that some in the latter group might well have been in the former group with more skill in the use of the steroids. Again, most of the failures were in the severely ill, but many such patients improved sufficiently to respond later to conventional therapy. Follow-up observation of 191 patients after drug treatment had been withdrawn showed that in 38% the response was still favourable—that is, continuing remission—and in 19% it was moderately favourable (occasional relapses but less often than before treatment).

The incidence of complications of colitis generally decreased during or after steroid treatment, although the trend could not be attributed entirely to this. The majority of patients with arthritis, erythema nodosum, and pyoderma gangrenosum were completely relieved of these conditions. Complications developing during or after treatment were generally seen in patients who had not had them before and usually when the steroid was given in low dosage or was completely withdrawn. Iritis and uveitis always improved with steroid treatment and no new case was seen. Although there appeared to be an increased incidence of haemorrhage, perforation, pericolicitis, carcinoma, and toxic megacolon, it was considered that these complications were not caused by the steroids alone, being more closely related to the severity of the disease. There was no increase in the incidence of perirectal abscess or fistula. The increased incidence of renal calculi was probably the result of the osteoporotic effect of inactivity and alterations in electrolyte balance as well as of the calcium effects of the steroids. There was an increased incidence of thrombophlebitis, but again this correlated better with inactivity and administration of intravenous infusions than with the steroid therapy.

As regards side-effects of steroid treatment, Cushingoid features were almost universal but were reversible after the drugs were withdrawn and were reduced by sodium restriction. Severe infections were the most undesirable complication (5 fatal cases) but, as the authors point out, they are common in severely ill patients. The development of osteoporosis was also a serious side-effect of prolonged steroid therapy, but it did not parallel completely the dosage or duration of administration of steroids, being detected sometimes within 3 months.

The authors conclude that steroid therapy does not increase the risk of complications of colitis and that some of the deaths at first attributed to this would probably have occurred in any event since the patients were severely ill. There was no increase in the incidence of peptic ulceration or intestinal perforation, and several patients with peptic ulcers were treated uneventfully. No difficulty was experienced in recognizing acute abdominal emergencies when these occurred during steroid therapy. There was little evidence that this medical management seriously delayed the initiation of surgery and the risks of operation were not increased. ACTH was considered to be the most potent drug, but the authors hesitate to prescribe it for severely ill patients with a low serum protein level and poor nutrition, in whom, probably, adrenal stimulation is maximal. There was no evidence that any benefit was to be gained from a combination of ACTH and steroids. Higher doses of ACTH than those administered originally are now recommended; the minimum necessary to induce remission is given at first and continued for a further month before the dosage is reduced.

A. Gordon Beckett

Cardiovascular System

321. **The Diagnosis of Cardiac Neoplasms.** (К диагностике опухолей сердца)
N. P. MALYSKIN. *Терапевтический Архив [Ter. Arkh.]* 34, 20-24, Feb., 1962. 21 refs.

In view of the fact that cardiac neoplasms can now be dealt with surgically, an early diagnosis has become of greater importance. Between 1946 and 1959 the author investigated 6 primary neoplasms of the heart, of which one was a fibrosarcoma and the other 5 myxomata; all were situated in the left atrium.

The symptoms resemble those of valvular disease of the heart, but the following signs are important as they may enable a differential diagnosis to be made: (1) the tendency of the patient to assume a horizontal position; (2) the sudden appearance of dyspnoea; (3) the presence of cyanosis; (4) retrosternal pains; (5) haemoptysis; (6) loss of consciousness when the position of the body is suddenly changed, especially on sitting up; (7) the sudden appearance of arrhythmia; (8) a change in the heart murmurs when the position of the body is changed; (9) embolism of vessels in the greater circulation; and (10) absence of any effect of treatment. An early diagnosis of primary neoplasms is possible in some cases. The author also discusses 24 cases of cancer of the lung in which there was secondary involvement of the heart.
H. W. Swann

322. **The Splitting of the Second Heart Sound in Normal Subjects and in Patients with Congenital Heart Disease**
M. M. AYGEN and E. BRAUNWALD. *Circulation [Circulation]* 25, 328-345, Feb., 1962. 15 figs., 30 refs.

This study is based on phonocardiograms obtained from 350 patients at the National Heart Institute, Bethesda, Maryland, and a particular study was made of the effect of respiration on the pulmonary second sound in 51 controls and 118 patients with atrial septal defect, of whom 31 were studied again after surgical closure of the defect.

In the normal subjects inspiration caused a prolongation of the right ventricular ejection time, increasing the interval QP_2 (from the start of ventricular depolarization to pulmonary valve closure) by an average of 32.6 milliseconds. Simultaneously the left ventricular ejection time usually shortened, QA_2 decreasing by an average of 5.2 msec. The "split" in the pulmonary second sound, A_2P_2 , thus increased by 37.8 msec. Release of breath after the Valsalva manoeuvre exaggerated this effect, A_2P_2 increasing by 49.7 msec. Patients with atrial septal defect have a widely split pulmonary second sound, which on auscultation appears uninfluenced by inspiration. The phonocardiographic recordings confirmed this, showing a mean A_2P_2 of 50.2 msec. in expiration which increased by only 4.6 msec. on inspiration. Release of breath after the Valsalva manoeuvre similarly increased A_2P_2 by only 4.7 msec. After closure of the defect a more normal pattern was restored, A_2P_2 being shorter in expiration and increasing on inspiration.

In normal subjects inspiration, or release of the Valsalva manoeuvre, causes an increased return of blood to the right

atrium, which prolongs the right ventricular ejection time; simultaneously, a reduced return from the pulmonary veins to the left atrium shortens the left ventricular ejection time, causing an audible increase in the "split" of the pulmonary second sound. The presence of a septal defect converts the two atria dynamically into a single chamber so that inequalities in the quantity of blood returning to each atrium are compensated for by a change in the shunt of blood crossing from right to left through the defect. In support of this explanation, blood samples from the pulmonary artery are shown to be less oxygenated in inspiration than in expiration, indicating a smaller left-to-right shunt in inspiration.
J. A. Cosh

323. **Assessment of Mitral Regurgitation by Dye Dilution Curves**

L. RESNEKOV. *British Heart Journal [Brit. Heart J.]* 24, 17-25, Jan., 1962. 8 figs., 18 refs.

Mitral regurgitation was assessed by the dye dilution technique in 50 consecutive patients at King's College Hospital, London, suffering from mitral valve disease but without severe aortic valve disease. Right-sided heart catheterization was carried out and with an ear oximeter in position Coomassie blue (0.5 to 1 mg. per kg. body weight) was injected rapidly into the main pulmonary artery. The final signal from the oximeter was led to a pen recorder with a sensitivity such that curves of 8 to 10 cm. at peak concentration were obtained. After replotting and extrapolation on semi-logarithmic paper, the Shillingford index was measured. The Shillingford or dispersal index is the ratio of the spread of the curve at one-tenth of its height to the appearance time.

The presence or absence of mitral regurgitation was established in all the cases and clinical assessment of the severity of the condition was compared with the dispersal index of the dye curve. The dispersal index in 7 subjects with normal hearts was used for control purposes. Of the 50 patients 23 underwent operation and the degree of regurgitation found by the surgeon was noted.

The dispersal indices in the patients with normal hearts were less than 3. Agreement between the dispersal index and clinical or operative findings was good only in cases of gross or moderate mitral regurgitation. In 11 out of 12 such cases the dispersal index exceeded 3.4, being over 4 in 8 of them. Agreement was poor in the 38 patients without or with only slight mitral regurgitation. High dispersal indices were obtained in 10 out of 16 patients without clinical evidence of regurgitation, which was confirmed at operation. It would seem that in cases in which there is clinical doubt about the degree of valvular incompetence and in which extra aid is most required the dispersal index is least helpful. The author states that the dye curves in valvular regurgitation are deformed, and there are good reasons for believing that this is not related only to the degree of regurgitation. It is probable that the deformity is produced by poor mixing of the dye in the left atrium and by the diastolic residual volume. "It remains to be seen whether sam-

pling of blood from the left atrium at the same time as injecting dye into the left ventricle will provide more accurate information about the degree of mitral regurgitation."

G. Clayton

324. Results of Surgical Treatment for Congenital Aortic Stenosis

F. H. ELLIS JR., P. A. ONGLEY, and J. W. KIRKLIN. *Circulation* [Circulation] 25, 29-38, Jan., 1962. 9 figs., 16 refs.

This paper from the Mayo Clinic gives the results of open operation, using extracorporeal circulation, in 47 cases of congenital aortic stenosis between April, 1953, and July, 1960. There were 33 cases of valvular, 11 of subvalvular, and 3 of supra-valvular stenosis. Valvular stenosis was usually treated by incision of the fused commissures, and subaortic stenosis by transaortic excision of the lesion. The over-all operative mortality was 13% (6% in valvular and 36% in subvalvular stenosis; there were no deaths among the 3 patients with supra-valvular stenosis).

Severe aortic incompetence did not develop in any patient operated on for valvular stenosis, though in some cases a diastolic murmur was present after operation. Rarely, however, was the transvalvular gradient completely eliminated by operation, although 90% of the surviving patients either were asymptomatic or had definite clinical improvement. Late (20 to 33 months) follow-up haemodynamic studies suggest that a persistent transvalvular gradient may regress in time.

A plea is made for early operation in cases of congenital aortic stenosis, before the sequelae of severe left ventricular hypertension become manifest. F. J. Sambrook Gowar

325. Aorticopulmonary Septal Defect

H. N. NEUFELD, R. G. LESTER, P. ADAMS JR., R. C. ANDERSON, C. W. LILLEHEI, and J. E. EDWARDS. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 12-25, Jan., 1962. 9 figs., bibliography.

The authors report a study of 6 cases of aorticopulmonary septal defect seen at the University of Minnesota Hospitals, Minneapolis. Structurally the cases differed from cases of persistent truncus arteriosus in that the aortic and pulmonary valves and ventricular septum were intact. Most defects lay about 1.5 cm. above the ostia of the coronary arteries. The largest defect measured 25 mm. and was seen in a girl of 11 years. A variety of other coexistent anomalies were present. The pulmonary arterioles showed medial hypertrophy.

Clinical findings resembled those of a large septal defect. All cases had a systolic murmur and 3 a diastolic murmur, but none had a continuous murmur. All had an accentuated pulmonary second sound. Definite cyanosis was present in one case. Systolic blood pressures ranged from 100 to 120 mm. Hg, and diastolic blood pressures from 0 to 70 mm. Electrocardiographic findings were not specific. Haemodynamic findings were similar to those of a large patent ductus arteriosus. The larger the defect, the more nearly did pressures on the right side of the heart equal those on the left. Specialized techniques of cardiac catheterization may be used in differentiating the condition from ventricular septal defect, patent ductus arteriosus, complete persistence of truncus arteriosus, and transposition of the great vessels. Aortography is also considered useful in differential diagnosis.

Operation was performed on 5 patients, total cardiopulmonary by-pass being used. The aorta is clamped distal to the defect, which is closed digitally while selective cardiac hypothermia is obtained by perfusing the proximal aorta. When cardiac arrest has occurred the defect is divided under direct vision and the aorta and pulmonary trunk are repaired. Of the 5 patients subjected to this procedure, 3 survived. D. Goldman

326. Relation between Ventilation and Haemodynamics of the Pulmonary Circulation in Congenital Heart Disease. (Beziehungen zwischen Ventilation und Hämodynamik des Lungenkreislaufes bei angeborenen Herzfehlern)

A. KRAUTWALD, A. LICHTERFELD, D. KOLMAR, H. HÄHNEL, J. GARTEN, and J. KIESSLING. *Klinische Wochenschrift* [Klin. Wschr.] 40, 125-129, Feb. 1, 1962. 1 fig., 49 refs.

Ventilatory function in relation to the haemodynamics of the pulmonary circulation was investigated in 92 patients with congenital heart disease seen at the Charité Hospital, Berlin. The respiratory measurements included determination of minute volume, vital capacity, timed vital capacity, and residual volume (by the nitrogen method), while haemodynamic tests carried out by means of cardiac catheterization included determination of lung circulation time, pulmonary arterial pressure, pulmonary capillary pressure, minute volume, and oxygen estimation.

It was found that in 23 patients with pulmonary stenosis ventilation was normal; in 55 patients with left-to-right shunt (atrial septal defect, ventricular septal defect, and ductus arteriosus) there was a slight reduction in ventilation with an increase in residual volume; greater disturbance of ventilation was found in 6 cases of Fallot's tetralogy and in 13 patients with septal defects and pulmonary hypertension. There was a statistically significant correlation between ventilation and pulmonary arterial pressure, but none with increased shunt volume. A. J. Karlish

327. The Risks of Dental Extraction during Penicillin Treatment

L. P. GARROD and P. M. WATERWORTH. *British Heart Journal* [Brit. Heart J.] 24, 39-46, Jan., 1962. 2 figs., 13 refs.

The authors of this paper from St. Bartholomew's Hospital, London, demonstrate the fallacy in the view, which must be held by many physicians, that teeth may be extracted during adequate penicillin treatment without the risk of streptococcal infection or re-infection of damaged heart valves. Apparently during such penicillin treatment relatively resistant streptococci appear very quickly in the mouth flora and bacteraemia resulting from tooth extraction may thus result in a highly resistant bacterial endocarditis.

Penicillin cover for tooth extraction should aim at maintaining a bactericidal concentration in the blood from the time of extraction and for some 8 hours or longer afterwards. This can be achieved by giving 100,000 units of soluble penicillin together with 300,000 units of procaine penicillin immediately before the operation, perhaps repeating the dose after 12 hours. If the patient is already receiving penicillin, for example, for the prevention of rheumatic fever, another bactericidal drug should be chosen to cover tooth extraction. Vancomycin in a single intravenous injection of 1 g. is suggested. In established bacterial endocarditis dental treatment should be undertaken preferably before or

within 24 hours of the start of penicillin administration. Should this be impracticable and extractions are required during treatment or shortly afterwards another antibiotic should be chosen for cover.

The authors state that "in any further observations on the subject it is important that the sensitivity to penicillin of streptococci, if cultivated from the blood during a relapse, should be re-tested by an accurate multiple dilution method".

T. Semple

328. Enterococcal Endocarditis: Lack of Correlation between Therapeutic Results and Antibiotic Sensitivity Tests

R. TOMPSETT and M. PIZETTE. *Archives of Internal Medicine* [Arch. intern. Med.] 109, 146-150, Feb., 1962. 1 fig., 8 refs.

Following reports that a combination of penicillin and streptomycin was more effective in the treatment of enterococcal endocarditis than either antibiotic alone, an attempt was made at Baylor University Medical Center, Dallas, Texas, to correlate *in-vitro* sensitivity studies on the bacteria with the ability to achieve a bacteriological cure of the patient. The enterococci used in the study were obtained from blood cultures of 4 patients who had been ill from one month to a year with enterococcal endocarditis. In one patient a course of penicillin and chlortetracycline had failed to be effective. *In-vitro* studies consisted in plotting growth curves of each culture in media containing penicillin and streptomycin separately, also penicillin and streptomycin combined, and a control medium with no antibiotic. The results of these studies showed that after 3 days' incubation penicillin had reduced the number of viable bacteria, but in no case did it completely kill the organisms. Streptomycin had no effect on the number of viable bacteria. In the cultures containing a combination of drugs, complete eradication of the bacteria occurred after 3 days in 2 cases, but viable bacteria were still present at 8 days in 2 others.

Clinically, however, the result of treatment with penicillin and streptomycin combined was satisfactory. Penicillin was used in a daily dosage of 6 to 8 million units, and streptomycin in a dose of 1 to 2 g. daily for 6 weeks. Bacteriological cure was achieved in all 4 cases, and the authors question the value of *in-vitro* tests in predicting the clinical result. This, they suggest, has become more relevant in view of the tendency to shorten antibiotic therapy in *Streptococcus viridans* endocarditis on the basis of the results of such tests. A 2-week course is now being tried in which, depending on the results of bacterial sensitivity to penicillin, it is proposed to use the 2 drugs in combination. If relapses after short courses of antibiotics are to be prevented, other criteria must be used.

J. S. Malpas

329. Nonbacterial Thrombotic Endocarditis: a Clinico-pathologic Study

W. E. BARRY and D. SCARPELLI. *Archives of Internal Medicine*, [Arch. intern. Med.] 109, 151-156, Feb., 1962. 3 figs., 18 refs.

Non-bacterial thrombotic endocarditis is a condition in which there is formation of sterile thrombi on the endocardium of a normal or damaged valve; these thrombi may give rise to emboli in the spleen, kidney, and brain. The condition is particularly associated with debilitating disease, especially metastatic carcinoma. A clinico-pathological study of 21 patients with this condition seen over a 12-year period has been carried out at Ohio State University College of Medicine, Columbus, Ohio. Among these were 14 men

and 7 women in late middle age and usually debilitated from metastatic carcinoma, leukaemia, or peptic ulceration. At necropsy, involvement of the mitral valve was found in 11 cases, of the aortic valve in 6 cases, and of both mitral and aortic valves in 4 cases. There was evidence of splenic, renal, or cerebral infarction in 9 of the 21 cases. In life, 4 out of the 13 patients with adequate records had been noted to have heart murmurs, and in a further 4 there was clinical evidence of infarction.

The vegetations showed no inflammatory reaction; they were sterile, and Aschoff nodules were carefully excluded. A typical vegetation contained capillaries, fibrin, erythrocytes, and platelets, together with some lipid material. Histochemical staining proved the absence of collagen in the vegetations and also demonstrated the similarity between the vegetations and the emboli.

The authors suggest that in debilitating disease non-bacterial thrombotic endocarditis should be considered when infarction of the brain, spleen, or kidneys occurs.

J. S. Malpas

330. The Effect of Intracardiac Acetylcholine Infusion upon Right Heart Dynamics in Patients with Rheumatic Heart Disease Studied at Rest

P. SAMET, W. H. BERNSTEIN, L. FERNANDEZ, and W. DE VICTORIA. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 32-42, Jan., 1962. 29 refs.

This paper reports observations on the effect of infusion of acetylcholine into the heart in 67 patients with rheumatic valvular disease at Mount Sinai Hospital, Miami Beach. During 79 right heart catheterizations acetylcholine was infused via the catheter at rates varying from 0.5 to 10 mg. per minute. Pulmonary and systemic arterial pressures and cardiac output were measured before and during infusion. Systemic arterial cannulation was performed with a Courmand needle, and cardiac output was estimated by the Fick principle.

Results showed a small significant decrease in pulmonary mean arterial pressure, least marked in cases of pulmonary hypertension. The authors conclude that this slight pulmonary vasodilator effect indicates that acetylcholine can do little to ameliorate the pulmonary hypertension of mitral stenosis.

D. Goldman

331. The Management of Cardiac Arrhythmias with Quinidine Polygalacturonate

R. TRICOT and P. NOGRETTE. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 215-221, Feb., 1962. 18 refs.

The authors describe, from the Lariboisière Hospital, Paris, the treatment with quinidine polygalacturonate of 26 patients with chronic arrhythmia. These included 21 with chronic atrial fibrillation, one with atrial flutter, and 4 with paroxysmal atrial fibrillation. Mitral valvular disease was present in 14 patients, 4 of whom had had commissurotomy. Eight patients were in cardiac failure. The patient with atrial flutter had not responded to any other treatment, and the 4 patients with paroxysmal fibrillation had an intolerance to conventional quinidine salts.

All patients were examined before and during treatment. Anticoagulant therapy was instituted and most were digitalized beforehand, but the digitalis was stopped at least 2 days before treatment with quinidine polygalacturonate was

started. This was administered in tablets of 0.275 g., and one tablet was given at the outset to test for intolerance. Treatment began with 2 tablets thrice daily for 1 to 3 days, increasing to 12 tablets daily for a maximum of 2 to 3 days or until sinus rhythm returned. The maintenance dose was 3 or 4 tablets daily.

All except one patient with chronic atrial fibrillation reverted to normal rhythm. Transient cardiac arrhythmias seen occasionally during the treatment disappeared with cessation of fibrillation. The drug had a moderate hypotensive action in 6 cases, but the blood pressure returned to normal when sinus rhythm was restored. No patient had diarrhoea, vomiting, or nausea. Any effect on the prothrombin time was masked by the anticoagulant therapy. Thus in this series quinidine polygalacturonate had a success rate of 95% and caused no serious side-effects.

E. H. Johnson

CORONARY DISEASE AND MYOCARDIAL INFARCTION

332. Effects of an Intravenous Infusion of a Potassium-Glucose-Insulin Solution on the Electrocardiographic Signs of Myocardial Infarction: a Preliminary Clinical Report

D. SODI-PALLARES, M. R. TESTELLI, B. L. FISHLEDER, A. BISTENI, G. A. MEDRANO, C. FRIEDLAND, and A. DE MICHELL. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 166-181, Feb., 1962. 20 figs., 40 refs.

In this paper from the National Institute of Cardiology, Mexico City, the authors describe the results of administering potassium together with insulin and glucose to patients with myocardial infarction. This treatment is based on the fact that in the normal heart the muscle fibres are kept polarized by the maintenance of a high ratio of intracellular to extracellular potassium, but when the muscle is injured by infarction the potassium gradient across the cell wall is reduced, so that the fibres become less excitable or even non-excitable. Thus if the intracellular potassium concentration could be increased, with restoration of the gradient of potassium across the cell membrane, an improvement in the excitability of the muscle fibres might be expected. The authors consider that this can be achieved by the intravenous administration of potassium together with insulin and glucose to facilitate the entry of the potassium into the cells. The method used was to give an intravenous infusion of 40 mEq. of potassium chloride and 20 units of soluble insulin in 1 litre of 10% glucose solution in water, the infusion being given at a rate of 3 to 4 ml. per minute, preferably through polyethylene tubing inserted high up a large antecubital vein. This could be safely carried out every other day in patients with recent myocardial infarction, provided they were not in shock and that renal function was not impaired. In a few cases the potassium was given by mouth.

In all, 10 patients with recent myocardial infarction, one with an old myocardial infarction, and 20 with chronic coronary insufficiency were studied. The effects of the treatment, which were most noticeable some hours after the infusion had been given, were judged by changes in the electrocardiogram. In 3 of the 10 recent cases the results were assessed as excellent, there being reduction of the amount of RS-T displacement following each infusion, and stabilization of the electrocardiogram at an earlier stage

than would be expected if the treatment had not been given. In the other cases the effects of the treatment were not so obvious. In some of the patients with anginal pain there was an improvement in the sense of well-being and relief of pain, but the number of patients studied was not large enough to permit of definite conclusions about symptomatic relief to be drawn. The authors conclude that the treatment described is safe, and is beneficial in a proportion of cases, and propose its wider use in patients with myocardial infarction.

M. Harington

333. Effect of Acute Myocardial Infarction Upon Serum Cholesterol Levels

H. Z. POMERANTZ. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 355-359, Feb. 24, 1962. 6 refs.

At the Jewish General Hospital, Montreal, the serum cholesterol level was determined in 30 patients with chronic coronary arterial disease and in 28 with acute myocardial infarction. The cholesterol level was found to be over 250 mg. per 100 ml. in all but 6 of the chronic cases (mean level 286 mg. per 100 ml.), whereas only 3 of the 28 patients with acute infarction had a level over 250 mg. per 100 ml., mean value for the group being 212 mg. per 100 ml. In 10 patients previously known to have a high serum cholesterol level, a fall in level was recorded during the acute phase. In describing 6 of these cases in more detail it is noted that the serum-cholesterol level usually fell between 2 and 5 days after the onset of acute infarction, remained low for 16 to 30 days or longer, and then began to rise again.

Some of the patients were given a low-fat diet while others remained on the normal hospital diet, but the fall in the serum cholesterol level was not related to the type of diet, and indeed occurred too quickly for this to have influenced it. In those patients in whom the cholesterol level fell with onset of acute infarction, the fall coincided with a rise in the erythrocyte sedimentation rate and in serum transaminase levels, indicating the occurrence of necrosis with inflammation of the myocardium. In 2 patients in whom the cholesterol level did not fall the serum transaminase level did not rise and the electrocardiogram showed no abnormal Q wave. The significance of this finding and its possible relation to stress and adrenal activity are discussed.

E. H. Johnson

334. Anticoagulant Treatment in 104 Male Cases of Acute Myocardial Infarction

T. E. GUMPERT. *Lancet* [Lancet] 1, 399-400, Feb. 24, 1962. 8 refs.

This is a study of the mortality in a group of 104 male patients with recent myocardial infarction who were seen at Sheffield Royal Hospital in the period 1950-9. Various schedules of treatment were employed, with and without anticoagulants. The lowest mortality occurred in those patients who received early and full treatment with anticoagulant drugs, and the highest mortality in those who had no anticoagulants. However, when the patients were grouped according to the gravity of illness on admission the mortality was found to be dependent almost entirely on this factor and to be largely independent of treatment. The only exception was that deaths within 3 days of the onset of cardiac pain were less frequent when early and full anticoagulant therapy was administered.

Bernard Isaacs

335. **A Clinicopathologic Study on the Feasibility of Direct Surgical Treatment of Occlusive Coronary Arterial Disease**
H. A. SWEDLUND, R. W. P. ACHOR, and J. E. EDWARDS.
Circulation [Circulation] 25, 292-299, Feb., 1962. 5 figs., 20 refs.

Endarterectomy is one of the surgical procedures by which coronary atherosclerosis can, theoretically, be relieved. To estimate how often it might justifiably be attempted, 112 fully documented case histories of patients aged 40 to 87 years were studied at the Mayo Clinic; in each case necropsy had been performed and the heart was available for detailed examination. The coronary arteries were examined at intervals of 3 to 4 mm., and reduction of the lumen by atheroma to under 50% was regarded as a significant obstruction. Such a condition was regarded as theoretically operable if (1) the outside diameter of the artery was 3 mm. or more at the site of the lesion, (2) the length of the stenotic lesion was under 5 cm., and (3) the distal coronary branches were not significantly involved.

In the cases studied 13 of the 90 men and 7 of the 22 women had an "operable pattern" of disease, that is, with operable lesions of the right, left, or circumflex arteries. Of the 13 men, only 2 were under 60 years of age and 6 were in the 7th decade, while of the 7 women none were aged under 60, and 2 were in the 7th decade. There were no particular features in the clinical histories or findings which would have enabled these patients to be selected for endarterectomy during life. A larger number of patients had a pattern of disease amenable to palliative surgery, that is, with some of the lesions operable and some not. This group included 48 men (12 under 60 and 15 in the 7th decade) and 10 women (2 under 60 and one in her 7th decade).

The [unhappy] conclusion is reached that coronary disease is commonly widespread in younger adults, especially men, and that few patients of suitable age are likely to be candidates for direct surgical relief of coronary obstruction.

J. A. Cosh

336. **Studies with a New Coronary Vasodilator Drug: Persantin**

D. KINSELLA, W. TROUP, and M. MCGREGOR. *American Heart Journal [Amer. Heart J.]* 63, 146-151, Feb., 1962. 24 refs.

This study, carried out at the Royal Victoria Hospital, Montreal, was designed to determine if the drug "persantin", a pyrimidine derivative, was of therapeutic value in patients suffering from long-standing angina pectoris. The investigation was in three parts: (1) In 6 patients (3 with typical angina pectoris) the oxygen saturation was determined by catheterization of the coronary sinus after intravenous administration of the drug. (2) In 12 anginal patients (19 trials) when pain and changes in the electrocardiogram (ECG) were produced after exercise, the intravenous effects of the drug were assessed in regard to the relief of pain and any improvement in the ECG pattern. (3) In 16 anginal patients persantin was given by oral medication over a long period (11 patients receiving a low dose (100 mg. daily) and 5 a high dose (225 mg. daily)).

By coronary sinus catheterization evidence was obtained that 20 mg. of persantin given intravenously might be expected to produce a significant increase in coronary flow for 10 to 20 minutes, even in subjects with ischaemic heart

disease. A similar dose given to patients with angina pectoris failed to prevent the occurrence of ischaemic changes in the ECG on effort, although in 6 of the 19 trials it appeared to prevent the onset of pain. By contrast 0.6 mg. of nitroglycerin sublingually prevented pain in 7 out of 7 exercise tests and prevented ischaemic changes in the ECG in 6 out of 7 tests. Persantin given orally in doses of 100 mg. per day appeared to have no therapeutic effect in angina pectoris. Dosage of 225 mg. per day produced gastro-intestinal symptoms in 2 subjects and gave no benefit over a period of 6 weeks in 3 others.

P. T. O'Farrell

337. **Sequential Trial of Isocarboxazid in Angina Pectoris**
A. P. GRANT. *British Medical Journal [Brit. med. J.]* 1, 513-515, Feb. 24, 1962. 1 fig., 24 refs.

Various monoamine oxidase inhibitors have been used to relieve angina pectoris, but controlled trials have tended to discredit them. The present trial, carried out at Belfast City Hospital, was of the double-blind, cross-over type, using isocarboxazid ("marplan") and a placebo, and each of the 55 patients taking part acted as his own control. Each treatment was given for 4 weeks, with a gap of 3 weeks between treatments. The dose was one tablet thrice daily before meals, equivalent to 30 mg. of isocarboxazid daily. The results were assessed at the end of each 4-week period on a purely subjective basis and were charted on a sequential trial chart.

Milder cases showed more response to the placebo, but more severe cases tended to respond to the drug. The result of the trial favoured isocarboxazid. Side-effects were insignificant, and the blood pressure and electrocardiogram were not altered.

[The rough subjective assessment is the weak part of this trial, and the author seems to be aware of this. The other doubt concerns the nature of the pharmacological action of isocarboxazid: is it on the coronary arteries or on the mental attitude to cardiac pain?]

T. B. Begg

BLOOD VESSELS

338. **Atherosclerosis of Arteries of Lower Limbs**

G. W. TAYLOR and A. R. CALO. *British Medical Journal [Brit. med. J.]* 1, 507-510, Feb. 24, 1962. 4 figs., 3 refs.

The natural history of atherosclerosis of the leg arteries was studied by following 412 patients at St. Bartholomew's Hospital, London, over a period of 3 to 12 years. Men accounted for 92% of the patients, and almost half were in their sixth decade when first seen. Of the 412 patients, 88 (21%) have died, 40% of the deaths being due to coronary occlusion and 11% to cerebrovascular disease. The average survival was 8 years in those under 50 and 4 years in those over 50. Hypertension was present in 114 patients (28%), angina in 71 (17%), and diabetes in 18 (4.5%).

The 3 main symptoms are said to be intermittent claudication, pain at rest, and gangrene; the last 2 symptoms are commoner if the arterial occlusion is distal to the popliteal artery.

Lumbar ganglionectomy was performed for the relief of 233 limbs which were the site of intermittent claudication only; in 95 (41%) of the limbs the claudication improved, but this was similar to the natural rate of improvement in unoperated limbs of comparable clinical state. Lumbar

ganglionectomy was performed for rest pain with or without minor necrotic lesions in 113 limbs; of these, 68 (60%) improved, in contrast to 24 (28%) of 84 similar limbs which were not operated upon. In several cases the operation was performed for severe rest pain and threatened major gangrene, but was of no benefit.

These findings confirm previous reports that lumbar ganglionectomy has no place in the treatment of intermittent claudication or of established gangrene, but is useful for mild or moderate rest pain and early nutritional changes in the feet.

The over-all amputation rate was 10%. The rate in hypertensive patients was only 5%, and the authors suggest that hypertension is a favourable factor so far as the limb is concerned [but not all series of cases substantiate this]. Other favourable signs were lack of complication of intermittent claudication, a presentation before the age of 65, and a high (aorto-iliac) lesion.

T. B. Begg

339. The Use of Certain Biochemical and Instrumental Methods in the Investigation of Patients with Atherosclerosis.

(О применении некоторых биохимических и инструментальных методов при исследовании больных атеросклерозом)

L. T. PJAJ, A. N. VAPRA, and Y. I. LOONEN. *Клиническая Медицина [Klin. Med. (Mosk.)]* 40, 67-72, Jan., 1962. 5 figs., 24 refs.

In patients with atherosclerosis the serum content of lipoproteins and chylomicrons (large molecules rich in fat but poor in protein) is raised. Estimation of the lipoproteins by electrophoresis, measurement of the turbidity of the serum after a fatty meal, and the transmission of the pulse wave by plethysmography were the methods employed by the authors in this investigation of 45 patients with atherosclerosis and 22 control subjects. The biochemical tests were carried out on the patients fasting and again 4 hours after a fatty meal consisting of 2 egg-yolks and sugar. The serum cholesterol and lecithin levels were also estimated, but the wide variation in results in both normal subjects and atherosclerotic patients and the comparatively small increase after the fatty meal made these estimations of little diagnostic value.

The serum content of β - and γ -proteins was shown to be raised, compared with that of the smaller molecular groups, and the increased ratio was more marked after a fatty meal. The same was true of the serum turbidity. The rate of transmission of the pulse wave was measured with a plethysmograph attached over the femoral artery and synchronized on an electrocardiographic recording, the interval between the R wave and the appearance of the pulse wave being carefully measured. Combining this reading with the index of serum turbidity after the fatty meal, the authors have worked

out a constant (D) based on the formula $D = \frac{100}{3} \times p - S$,

where p is the time in seconds between the R wave and pulse wave, and S the level of turbidity (in units) of the serum after a fatty meal. This constant lay between 1.7 and 3.0 in the atherosclerotic patients, whereas in the healthy controls it ranged from 4.0 to 6.0. The factor "p" in the above formula was lower in the atherosclerotic group, that is, there was always acceleration of the pulse wave. The authors consider that in view of the simplicity of the method, it is a useful diagnostic aid.

L. Firman-Edwards

340. Surgery for Coarctation of the Aorta: a Review of 500 Cases

S. R. SCHUSTER and R. E. GROSS. *Journal of Thoracic and Cardiovascular Surgery [J. thorac. cardiovasc. Surg.]* 43, 54-70, Jan., 1962. 7 figs., 22 refs.

The authors present a review of 505 cases of coarctation of the aorta treated surgically at the Children's Hospital Medical Center (Harvard Medical School), Boston, during the past 15 years. In this series the mortality was 4% and the morbidity also 4%.

One of the many important points in surgery to which the authors draw attention was adequate mobilization of the aorta on either side of the coarctation. Hypertension, often reported by other workers, was found in only 1% of these patients and it was possible to establish end-to-end anastomosis in the majority of cases. In only 14% of cases was the insertion of a graft required; the presence of an associated aneurysm (57 cases) did not always necessitate resection of a long length of aorta. The influence of age on the results is also pointed out, the optimum age for operation being between 8 to 20 years, though cases in patients up to the age of 50 were undertaken. Post-operatively the relief of hypertension was regarded as a satisfactory indication of a good result, as also was a decrease in the heart size, the latter returning to normal in 67% of the series.

[If the authors' wide experience is to be adequately appreciated this authoritative review should be read in full.]

T. Holmes Sellors

341. Problems Associated with Long-term Anticoagulant Therapy; Observations in 139 Cases

J. W. POLLARD, M. J. HAMILTON, N. A. CHRISTENSEN, and R. W. P. ACHOR. *Circulation [Circulation]* 25, 311-317, Feb., 1962. 6 refs.

This review from the Mayo Clinic is concerned with the practical difficulties and deficiencies of long-term anticoagulant therapy; it is not concerned with its protective value. In all, 136 periods of therapy of an average duration of 18 months are analysed, a total of 91 men and 48 women with a mean age of 59 years (range 22 to 84 years) being treated. The indications for treatment included cardiac infarction in 43% of cases and cerebral vascular disease in 31%. Dicoumarol was the anticoagulant used in all cases, the dose being regulated by the results of a modified Quick one-stage prothrombin test performed on the average every 14 days, the aim being to keep prothrombin activity between 10 and 30% of normal. The usual daily dose of dicoumarol varied between 25 and 125 mg.

An effective control of prothrombin time, that is, maintenance of the intended effect in at least 4 out of 5 estimations, was achieved in only 57% of the cases (omitting the first 2 months of treatment or the periods of adjustment necessitated by surgery). Haemorrhage of some degree occurred in one-third of the patients and of the 15 major episodes 3 in the form of cerebral haemorrhage were fatal; older patients and those with hypertension were at greater risk in this respect than the remainder. The prothrombin activity was within the intended range at the time of 69% of the episodes of haemorrhage. Thrombosis or embolism occurred 23 times, although over half of these patients were correctly controlled. Surgery presented little difficulty, prothrombin activity being brought to normal for the

purpose; only one patient suffered a minor cerebral thrombosis postoperatively.

Some 16% of those stopping treatment did so for non-medical reasons; an increased tendency to thrombosis or embolism was noted after the withdrawal of anticoagulant therapy. In spite of all reasonable care, therefore, the desired effect on prothrombin activity was maintained in less than two-thirds of these patients, and even then this was no guarantee against thrombosis, embolism, or haemorrhage.

J. A. Cosh

HYPERTENSION

342. The Hemodynamics in Labile Hypertension

R. H. EICH, R. J. PETERS, R. P. CUDDY, H. SMULYAN, and R. H. LYONS. *American Heart Journal* [Amer. Heart J.] 63, 188-195, Feb., 1962. 14 refs.

At the State University of New York Upstate Medical Center, Syracuse, 73 patients (52 under the age of 50 and 21 over this age) with labile hypertension were studied haemodynamically by determining the cardiac output and the degree of peripheral resistance. The cardiac output was estimated by the dye-dilution method, of Hamilton and Stewart with radioactive iodinated human serum albumin as indicator. The total peripheral resistance was calculated in dynes from a formula in which the factors were mean blood pressure and cardiac output (in ml. per second) multiplied by 1,332. The mean blood pressure was taken to be the pulse pressure plus diastolic pressure. For comparison these results were tabulated against similar investigations carried out on 28 non-hypertensive patients in the same age groups.

In the labile hypertensive subjects two haemodynamic patterns were observed: (1) a high output and low resistance, and (2) a normal cardiac output and a raised peripheral resistance. These findings afforded some theoretical and clinical evidence that a high cardiac output may indicate a milder degree of hypertension and less likelihood of the development of fixed essential hypertension. Final proof of this awaits the results of a long-term follow-up and such a study is now under way.

P. T. O'Farrell

343. Effect of Alpha-methyl DOPA in Severe and Malignant Hypertension

P. J. CANNON, R. T. WHITLOCK, R. C. MORRIS, M. ANGERS, and J. H. LARAGH. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 673-681, March 3, 1962. 2 figs., 30 refs.

The authors report from the Presbyterian Hospital, New York, a study of the methylated derivative of 3:4-dihydroxyphenylalanine (methyl dopa), an inhibitor of decarboxylation, in the treatment of 33 hypertensive patients. A significant reduction in blood pressure in both the erect and supine positions occurred in 31 patients with a dose of 0.5 to 8 g. daily. The 2 patients who proved resistant had previously undergone bilateral surgical sympathectomy. The hypotensive action of the drug began 2 to 4 hours after an oral dose and the medication was given 2 to 4 times daily. Patients with severe azotaemia were sensitive to relatively small doses of methyl dopa. Tolerance developed in some patients, but was such as to require a change of treatment in only 2 of them. The main side-effect was lethargy, which occurred in 25 patients. Despite treatment 13 of the 33

patients are known to have died; of these 8 had malignant hypertension.

Methyl dopa had no effect on sodium balance or aldosterone secretion in the 5 patients in whom this was studied, while in regard to renal clearance of inulin and PAH, measured in 5 patients before and after treatment, no significant changes were seen. Urinary excretion of 3-methoxy-4-hydroxy-mandelic acid (VMA) was determined before and after methyl dopa in 5 hypertensive patients and one normotensive subject. Depression of VMA excretion was not observed and thus there was no support for the concept that the drug diminishes noradrenaline synthesis. Furthermore, MK-485 which has been shown *in vitro* to have a 100- to 1,000-fold greater decarboxylase inhibiting activity, had less antihypertensive activity than methyl dopa.

[This new drug clearly deserves wider trial. The high death rate (13 out of 33 patients) probably reflects the high proportion of patients already uraemic when treatment began, but it does not altogether support the view that this drug is suitable for the treatment of patients with malignant hypertension.]

C. T. Dollery

344. Clinical and Chemical Studies with α -Methyl-dopa in Patients with Hypertension

L. GILLESPIE JR., J. A. OATES, J. R. CROUT, and A. SJOERDSMA. *Circulation* [Circulation] 25, 281-291, Feb., 1962. 5 figs.

Studies at the National Heart Institute, Bethesda, Maryland, on 52 hypertensive patients have shown that α -methyl-3:4-dihydroxy-DL-phenyl-alanine (DL- α -methyl dopa) has a hypotensive and sedative effect, and that this is produced by the laevo- and not by the dextro-isomer. When given by mouth the drug produces this effect in 1 to 2 days, and injected intravenously acts in some 10 hours. Oral doses of between 0.75 and 4.0 g. daily produced considerable falls in blood pressure in the standing position (up to 40 mm. Hg. reduction in mean blood pressure) and sometimes a fall in the recumbent position also.

A trial of the laevo-isomer ("aldomet") over periods of 3 to 9 months in daily doses of 0.75 to 3.0 g., with or without the addition of chlorothiazide, produced a sustained hypotensive effect without development of tolerance. A few patients were troubled by drowsiness, and with the DL mixture there were 2 cases of depression and 2 of febrile reaction. It is suggested that the drug probably acts by sympathetic blockade either centrally or peripherally, and this may be related to the depletion of noradrenaline in the brain and sympathetic fibres reported elsewhere.

J. A. Cosh

345. Alpha Methyl Dopa in Treatment of Hypertension

R. O. H. IRVINE, K. P. O'BRIEN, and J. D. K. NORTH. [Lancet] 1, 300-303, Feb. 10, 1962. 2 figs., 11 refs.

Fifteen hypertensive patients were given alpha methyl dopa in doses varying from 0.75 g. to 3 g. daily for 16 weeks, with short periods on placebo at the beginning and near the end of the trial. The average falls in blood-pressure were 36/23 mm. Hg. standing and 31/18 mm. lying. Side-effects included dry mouth, sleepiness, loss of energy, and indigestion; but they were mild and of short duration. The minor nature of side-effects, together with the significant hypotensive action particularly in the lying position, makes alpha methyl dopa a valuable new drug in the treatment of high blood-pressure. —[Authors' summary.]

346. Reactivity of Renal and Systemic Circulation to Vasoconstrictor Agents in Normotensive and Hypertensive Subjects

E. A. GOMBOS, W. H. HULET, P. BOPP, W. GOLDRING, D. S. BALDWIN, and H. CHASIS. *Journal of Clinical Investigation* [J. clin. Invest.] 41, 203-217, Feb., 1962. 5 figs., 34 refs.

This report from the New York University School of Medicine and the Bellevue Hospital, New York, describes a study of the effects of adrenaline and noradrenaline on the resistance of the renal and systemic blood vessels in 16 normotensive subjects and 16 patients with relatively mild degrees of essential hypertension, all except 2 being female. Adrenaline or noradrenaline was infused at successively increasing rates, up to 10 μ g. per minute in the patients and up to 30 μ g. per minute in the controls, and the effect of the infusions on systemic blood pressure, glomerular filtration rate (inulin clearance), and renal plasma flow (clearance of PAH) observed. From the values obtained for these parameters the renal vascular resistance was calculated.

The results obtained with infusions of 10 μ g. per minute—the largest dose for which data were available in all subjects—were used for comparison between the two groups. With both adrenaline and noradrenaline there was no significant difference in the amount (about 20%) by which renal plasma flow was reduced in the hypertensive and normotensive patients. Glomerular filtration rate was not altered in either group. The mean systemic blood pressure rose by a comparable amount after noradrenaline in both groups, and the increases in calculated renal vascular resistance were also similar. The authors conclude that their results demonstrate equal vasoconstrictor reactivity of the arterioles in normotensive and hypertensive subjects, and that their observations are contrary to the thesis that essential hypertension might be related to increased sensitivity of the blood vessels to circulating noradrenaline.

In an extension of this study, a few of the subjects (4 normotensive and 8 hypertensive) were given a restricted sodium intake (250 mg. of NaCl daily) for 8 to 45 days. There was no evidence in this small number of patients that sodium restriction caused any decrease in vascular reactivity to noradrenaline or adrenaline in either the hypertensive or normotensive group, and in fact the sensitivity to noradrenaline was somewhat enhanced in both groups.

M. Harington.

347. Guanethidine, a New Antihypertensive Agent: Experience in the Treatment of 36 Patients with Severe Hypertension

A. SCHIRGER and R. W. GIFFORD JR. *Proceedings of the Staff Meetings of the Mayo Clinic* [Proc. Mayo Clin.] 37, 100-108, Feb. 14, 1962. 3 figs., 17 refs.

At the Mayo Clinic 36 patients with blood pressures ranging from 208/134 mm. to 220/152 mm. Hg (group averages) were treated with guanethidine in the form of "ismelin". Of the 36 patients, 22 had left ventricular hypertrophy, 4 congestive heart failure, 3 myocardial infarction, and 4 cerebral infarction. The treatment of 5 patients was discontinued within 14 days on account of syncope, rash, gastrointestinal complaints, or poor cooperation. The remaining 31 (9 women and 22 men) were followed up for 2 to 15 (average 7.2) months.

Treatment was initiated with a daily dose of 12.5 to 25.0 mg. given usually at bedtime. If the blood pressure failed

to respond within 3 days the dose was increased by 12.5 or 25 mg. every 3 or 4 days until it did. The average daily dose in the last month of treatment was 95.2 mg., but with wide individual range (in one case it reached 400 mg.). In a few cases the daily dose was divided. Patients were trained to take their own blood pressures (sitting and standing) at least twice daily. In calculating results the sitting blood pressures during the last month of treatment were compared with those before treatment, and in many cases also with those obtained during a previous antihypertensive regimen with some other drug.

Four of the patients died (one from an accident and the others from cardiac or renal failure) and in 2 treatment was discontinued because of alimentary disturbances. Of the remainder, those treated with guanethidine alone showed an average reduction in mean blood pressure of 24% (208/134 mm. to 154/100 mm. Hg). Some patients had in addition a thiazide diuretic, and these showed an average reduction of 22% (221/136 mm. to 157/101 mm. Hg). Another group given multiple agents as well as guanethidine had an average reduction of 16% (220/152 mm. to 190/120 mm. Hg).

Comparisons with the results obtained with other forms of treatment in the same patients are very interesting. Those treated with guanethidine alone showed an average reduction in mean blood pressure of 15% below the results obtained by previous treatment (174/115 mm. to 146/100 mm. Hg). When guanethidine was combined with thiazide the corresponding reduction was 13% (188/121 mm. to 161/103 mm. Hg). Although the results obtained when guanethidine was combined with thiazide seem slightly less favourable than those with guanethidine alone, it should be noted that the average initial pressures in the former groups were somewhat higher than those in the latter. The authors favour the addition of thiazide diuretics on the grounds that these facilitate a reduction in the maintenance dose of guanethidine for some patients.

The most common side-effects noted during treatment were orthostatic fall in blood pressure, weakness, and diarrhoea; 4 men experienced loss of potency. None of these effects amounted to a serious contraindication. One peculiarity which was observed with guanethidine was a consistent diurnal variation in the blood pressure, with the lowest level in the morning followed by a rise, often steep, in the afternoon. This feature remained unaffected by spacing of the doses.

The authors conclude that, "although guanethidine is not the ideal antihypertensive agent, its administration results in a selective blockade of the sympathetic nervous system which is a significant advance in medical treatment" [a conclusion with which one feels bound to agree].

Rex Matthews

348. The Effect of Angiotensin on Urine Flow and Electrolyte Excretion in Hypertensive Patients

J. J. BROWN and W. S. PEART. *Clinical Science* [Clin. Sci.] 22, 1-17, Feb., 1962. 8 figs., 21 refs.

In 15 male and 6 female patients suffering from hypertension due to various causes, including stenosis of one renal artery in 6 cases and probable chronic pyelonephritis in 5, but of no ascertainable cause in a further 6, the effect of infusing synthetic angiotensin on renal function was studied at St. Mary's Hospital, London. Before the infusion the pa-

tients were hydrated, the degree of hydration being kept as constant as possible. The clearance of inulin and para-amino hippuric acid (PAH) was measured before, during, and after the angiotensin infusions. The results are presented in detail in tables and figures.

The effect of angiotensin varied somewhat according to the height of the diastolic arterial pressure. In 17 patients this was over 120 mm. Hg and in 16 of these a diuresis occurred. At the same time both the systolic and diastolic pressures usually rose, but in some patients a diuresis took place in the absence of any change in blood pressure. The diuresis was generally accompanied by an increase in electrolyte excretion and by small changes in the clearance of inulin and PAH. In normal subjects and in patients with less severe hypertension angiotensin produced an anti-diuresis, though it also produced an anti-diuresis in one patient with a high diastolic pressure. The hypertension was treated by surgical means in the cases of arterial stenosis, and by medical means in the other cases. For some months after the blood pressure had been reduced to within normal limits the response to angiotensin infusions remained unchanged, but later it changed to that in normal subjects, that is, an anti-diuresis. Several hypotheses which could account for the results are discussed, but there appears to be no simple interpretation of the reactions to angiotensin.

[The original article should be read by those interested in this subject.] W. H. Horner Andrews

349. Mechanisms in Essential Hypertension

M. MENDLOWITZ, S. E. GITLOW, R. L. WOLF, and N. E. NAFTCH. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 100-106, Jan., 1962. Bibliography.

PERIPHERAL VASOMOTOR RESPONSES

350. Raynaud's Phenomenon

G. DE TAKATS and E. F. FOWLER. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 1-8, Jan. 6, 1962. 10-figs., 21 refs.

The progress of 66 patients with Raynaud's phenomenon who were observed over a period of 1 to 25 years is discussed in this paper from the University of Illinois College of Medicine and Presbyterian-St. Luke's Hospital, Chicago. It was found that of these 66 patients 20 had peripheral vascular disease and 35 had collagen disease, either scleroderma or disseminated lupus erythematosus. Collagen disease was often evident only many years after the onset of Raynaud's phenomenon. In 7 patients there was evidence of vasomotor hyperactivity, while 7 showed abnormalities in the electroencephalogram somewhat similar to those of psychomotor epilepsy. Abnormal clumping of erythrocytes or precipitation of globulin and "a sludge effect" causing a blockage of arterioles were observed in 4 patients.

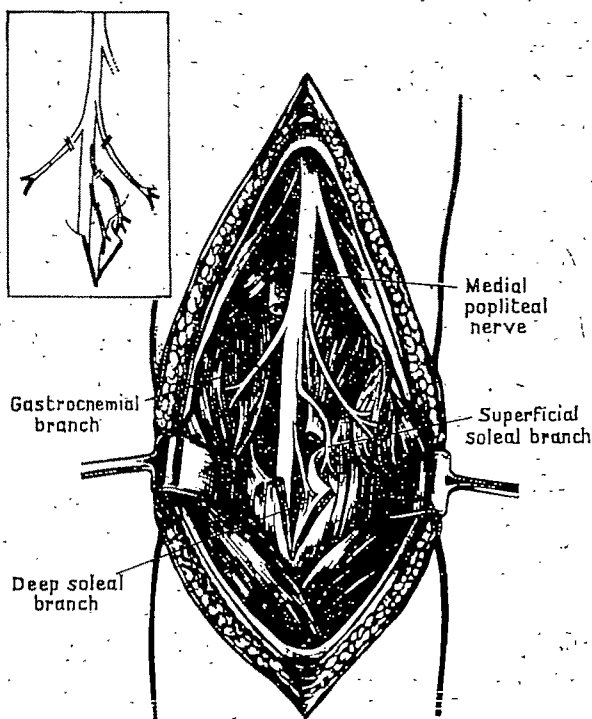
The treatment of this condition is briefly reviewed. There was no improvement with any vasodilator drugs. Sympathectomy was carried out on 18 only of the 66 patients, a total of 40 operations being performed with "a success rate of only 65%". The reasons for failure are discussed. The results of operations performed in the presence of peripheral arterial disease have been excellent. I. McLean Baird

351. Total Gastrocnemius and Soleus Denervation in the Treatment of Intermittent Claudication

A. MARSTON and F. B. COCKETT. *Lancet* [Lancet] 1, 238-241, Feb. 3, 1962. 1 fig., 6 refs.

This report from St. Thomas's Hospital, London, deals with 15 cases in which denervation of the calf muscles, combined in 9 cases with lumbar sympathectomy, was undertaken for intermittent claudication. In any series of cases of peripheral vascular disease with calf-muscle ischaemia there is always a considerable group of patients unsuitable or unfit for direct vascular surgery. Lumbar sympathectomy is unpredictable in its effects and may indeed worsen the claudication. Tenotomy of the tendo achillis is easily performed, but, in the authors' opinion, the postoperative gait is bad, also recurrence of pain due to reunion of the tendon occurs very frequently.

The authors have followed Boyd in dividing the nerve supply to the gastrocnemius and soleus (see diagram).



Exposure at operation. Inset shows nerves sectioned.

This anaesthetizes and paralyzes the muscles; it therefore diverts the limited arterial flow to other muscle groups and to the foot. It alters the mechanics of walking, the tibialis posterior and toe flexors taking over the functions of plantar flexion of the ankle. Full anatomical and operative details of the procedure are given. The most serious postoperative complication was deep calf vein thrombosis, which occurred in 2 cases. The final results of denervation, with or without lumbar sympathectomy, compare very favourably with those of tenotomy, with or without sympathectomy. Palliative surgery has a useful place in the treatment of claudication, and total denervation of the gastrocnemius and soleus muscles deserves further trial. J. V. Crawford

Clinical Haematology

352. An Investigation of Refractory Anaemias

C. W. H. HAVARD. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 21-55, Jan., 1962. Bibliography.

From a study of 24 cases of refractory anaemia seen at St. Bartholomew's Hospital, London, the author distinguished four clinical types. (1) In 4 patients the anaemia was normocytic or macrocytic, with no reduction in the leucocyte or platelet count. The bone marrow showed normoblastic hyperplasia, but megaloblastic change was present initially in one case and appeared subsequently in another, while myeloid proliferation developed in 2 cases. Pigment excretion was increased, and erythrocyte survival was normal. Disappearance of radioactive iron (^{59}Fe) from the plasma was rapid and its reappearance in the erythrocytes was slow and incomplete. Cases of this type are considered to be chronic forms of erythraemic myelosis. (2) In a further 4 patients there was pure red-cell anaemia or pancytopenia associated with a hypoplastic marrow. Pigment excretion was increased and erythrocyte survival reduced. The disappearance of ^{59}Fe from the plasma was slow and its reappearance in the erythrocytes subnormal. The Coombs test was positive. It is suggested that in these cases the anaemia is caused by autoimmune damage to the marrow. (3) The 3rd type was seen in 8 patients. In this group pure red-cell anaemia or pancytopenia was associated with a cellular marrow. Disappearance of ^{59}Fe from the plasma was variable, but its reappearance was incomplete. Erythrocyte survival was reduced and the Coombs test was negative. The cause of the anaemia was obscure; in 2 cases hypersplenism may have been responsible, in others it may have been caused by permanent damage to the marrow associated with a haemolytic state, while in still others the anaemia may have been pre-leukaemic. (4) This group (8 patients) was characterized by pancytopenia, an acellular bone marrow, slow disappearance of ^{59}Fe from the plasma, and impairment of its reappearance in erythrocytes; there was no evidence of haemolysis. Cases of this type are considered to be examples of true aplastic anaemia. It is suggested in conclusion that since the term "refractory anaemia" covers a number of entities its use should be abandoned.

[This interesting paper should be consulted in the original for technical and clinical details.] J. L. Markson

353. Changes in the Blood after Partial Gastrectomy with Special Reference to Vitamin B₁₂. I. Serum Vitamin B₁₂, Haemoglobin, Serum Iron, and Bone Marrow

D. J. DELLER and L. J. WITTS. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 71-88, Jan., 1962. 6 figs., bibliography.

The investigation here reported from the Radcliffe Infirmary, Oxford, was designed primarily to ascertain the incidence of vitamin B₁₂ deficiency in 265 patients one to 12 years after they had undergone partial gastrectomy. In 38 patients (14%) the serum vitamin B₁₂ level was below 150 μg . per ml., which is the lower limit of normal for the method used. The decline in the levels of the vitamin in the serum was associated with the time interval after gastrectomy, the steepest fall occurring during the first 6 years.

Age and sex did not influence the vitamin B₁₂ level, nor was it related to the amount of stomach resected, the occurrence of the dumping syndrome, bilious vomiting, or loss of weight. Subnormal serum levels of the vitamin were found more often after the Polya operation (18.9%) than after the Billroth-I operation (10.1%), and the incidence of low levels was greater in cases in which the resected stomach had shown histological changes of chronic gastritis.

Serum iron values in the 265 patients after gastrectomy ranged from 6 to 160 μg . per 100 ml., with a mean of 77 μg . per 100 ml. One-third of the values for iron were below the lower limit of normal, but the values were not related to the time interval after operation. There was a highly significant correlation between the serum iron level and the haemoglobin value, but 15% of patients, nevertheless, had serum iron values of less than 60 μg . per 100 ml. and haemoglobin levels of more than 13.6 g. per 100 ml. In 54 (20.4%) of the patients who were anaemic (39 men and 15 women) the anaemia was due to deficiency of vitamin B₁₂ in 4 cases, to deficiency of iron in 38, and to deficiency of both in 12. Megaloblastic anaemia was detected in 4 patients (1.5%) and partial megaloblastic change in the marrow in 14 (5.3%); 2 of these 18 patients were found to have subacute combined degeneration of the cord 10 years after partial gastrectomy. Megaloblastic anaemia after partial gastrectomy in this series was therefore not rare. Suggested reasons for the high incidence are: (1) examination of these patients up to 12 years after operation; (2) estimation of the serum vitamin B₁₂ level as a screening test; (3) frequent examination of the marrow; and (4) examination of the marrow in a number of cases after treatment with iron, which unmasked the megaloblastic change.

J. L. Markson

354. Changes in the Blood after Partial Gastrectomy with Special Reference to Vitamin B₁₂. II. The Cause of the Fall in Serum Vitamin B₁₂

D. J. DELLER, W. C. D. RICHARDS, and L. J. WITTS. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 89-102, Jan., 1962. 2 figs., 43 refs.

From the group of 265 patients previously subjected to partial gastrectomy [see Abstract 353] 41 patients were selected for further study for the following reasons: subnormal or borderline serum vitamin B₁₂ levels; iron-deficiency anaemia; diarrhoea; and stomal ulcer. Absorption of radioactive vitamin B₁₂ was determined by measuring the faecal excretion after an oral dose of 0.5 μg . of the labelled vitamin. Of the 41 patients, 16 excreted more than 46% of the test dose, indicating defective absorption; this, however, was improved in 15 cases by the addition of a small dose of intrinsic factor. In the remaining case absorption was improved by a larger dose of intrinsic factor, but not by tetracycline. Defective absorption of radioactive vitamin B₁₂ was commonly associated with low levels of the vitamin, but 50% of the patients with a serum vitamin B₁₂ level below 150 μg . per ml. absorbed the test dose normally. Faecal radioactivity was uninfluenced by the site of the ulcer or by the operative procedure. Steatorrhoea was found in 22 of the 41 patients, and more often after the Polya than after the

Billroth-I operation. No correlation was found between the faecal excretion of fat and faecal excretion of labelled vitamin B₁₂.

The augmented histamine test was performed in 36 patients and revealed the presence of achlorhydria in 26 cases and hypochlorhydria in 8. Of 20 patients with normal vitamin B₁₂ absorption, achlorhydria was found in 12, hypochlorhydria in 6, and normal acid secretion in 2. Of 16 patients with impaired absorption of the vitamin, 14 had achlorhydria and 2 hypochlorhydria. Impaired vitamin absorption did not occur in association with normal acid secretion. The mean excretion of urinary pepsinogen in 38 patients after partial gastrectomy was significantly greater than in normal subjects, but was higher than in patients with pernicious anaemia; the excretion of this substance was not related to the type of operation. Of 16 patients with impaired excretion of labelled vitamin B₁₂, 9 had reduced excretion of urinary pepsinogen, but this excretion was normal in the remaining 7 patients, 6 of whom had achlorhydria and megaloblastic change in the marrow. In 20 patients subjected to gastric biopsy the gastric mucosa was found to be abnormal, the changes ranging from gastritis with mild atrophy to gastric atrophy. The severity of the atrophic changes could not be correlated with the site of the ulcer, the type of operation, anaemia, iron deficiency, subnormal serum vitamin B₁₂ levels, achlorhydria, defective absorption of radioactive vitamin B₁₂, or megaloblastic change in the marrow. Jejunal biopsy, performed on 18 patients, showed the jejunal mucosa to be normal in 6 cases and abnormal in 12. Although shortening with broadening of the villi was present the gross villous atrophy of idiopathic steatorrhoea was not seen. The histological changes in the jejunum could not be correlated with steatorrhoea or with defective absorption of vitamin B₁₂.

The authors consider that the main cause of the reduction of the serum vitamin B₁₂ levels after partial gastrectomy is loss of intrinsic factor resulting from removal of part of the gastric mucosa and atrophy of the remainder. Other possible factors discussed are inadequate diet, inadequate stimulation of the secretion of intrinsic factor due to rapid emptying of the stomach, faulty binding of vitamin B₁₂ by intrinsic factor, decreased proteolysis in the stomach with consequent inability to split off vitamin B₁₂ from food, disturbance of the entero-hepatic circulation of the vitamin, jejuno-ileal insufficiency, and bacterial growth in the afferent loop after the Polya operation. J. L. Markson

355. Familial Neonatal Leukaemia

W. A. B. CAMPBELL, A. L. MACAFEE, and W. G. WADE. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 93-98, Feb., 1962. 6 figs., 19 refs.

The authors of this paper from the Royal Belfast Hospital for Sick Children describe a sibship of 6, of whom 2 died from acute leukaemia. A third child, for whom no details were available, died at home at about 4 weeks of age after an illness the course of which was similar to that of the 2 children who died. In both the established cases leukaemia was diagnosed in the first few weeks of life. The leukaemia was considered to be monocytic in one case and, probably, myeloid in the other. In one case volvulus of the small intestine occurred during life and at necropsy histological changes in the pancreas suggested early fibrocystic disease. Leukaemic involvement was found at necropsy in bone

marrow and lymph nodes in one case and in bone marrow only in the other. Evidence of erythrophagocytosis was seen in bone marrow and spleen in both cases. Chromosome studies were carried out on blood and skin samples from one of the patients and on the skin cells of both parents. No chromosome abnormality was found in either the patient's peripheral blood or skin or in the skin samples from the parents. There was no other family history of leukaemia and the parents were unrelated. The authors briefly review the reported instances of familial leukaemia and suggest that the cases they describe probably represent the first recorded ones of familial leukaemia occurring in the neonatal period.

A. G. Baikie

356. Prognostic Value of Uric Acid Excretion on Steroid Therapy of Acute Leukemia

E. SHANBROM. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 13-19, Jan., 1962. 5 figs., 11 refs.

The 24-hour urinary uric acid excretion was determined by the spectrophotometric method of Caraway on 53 occasions before and after treatment with prednisolone in 41 patients suffering from acute leukaemia (granulocytic in 14, lymphocytic in 22, monocytic in 4, and of plasma-cell type in one). The patients were allocated by the "double-blind" method to receive either 50 or 500 mg. of the steroid daily; in a few cases as much as 4 or 5 g. per day was given. Pretreatment values for uric acid excretion were usually below 1 g. per 24 hours. In patients who responded promptly to the treatment prednisolone produced a striking increase in uric acid excretion of up to 9 or 10 g. in the first 24 to 72 hours, this being usually, but not necessarily, associated with a fall in the total leucocyte count; it is noted, however, that the excretion level paralleled more closely the dosage of prednisolone. All the patients showing a markedly increased urinary uric acid excretion went into remission, while a slight increase in excretion was associated with a partial remission and an absence of increase with no remission. Myelomonocytic leukaemia seems not to respond to corticosteroids.

This study thus shows that determination of the 24-hour urinary uric acid excretion gives valuable early evidence of the patient's probable responsiveness to steroid therapy and is of particular value in cases of aleukaemic leukaemia, in which remission may often be difficult to assess.

R. B. Thompson

357. The Treatment of Chronic Myeloid Leukaemia with Myelosan. Immediate and Remote Results. (Лечение миелосаном больных хроническим миелолейкозом)

N. JA. ŠVEDOV. *Советская Медицина* [Sovetsk. Med.] 25, 11-17, Feb., 1962. 24 refs.

"Myelosan" ("myleran"; busulphan) was used in the treatment of 32 cases of chronic myeloid leukaemia over a period of 4 years, dosage being 2 to 4 mg. a day; the average total dose of a course of treatment was 240 mg., and in the present series from one to 5 courses were given. Two patients failed to respond to the treatment, in another case there was a short-term improvement, while in a 4th case the condition of the patient deteriorated. Of the remaining 28 patients, 7 died during the period of observation. However, of the 21 patients who responded favourably to the treatment, 12 were later able to work and the condition of the other 9 was satisfactory.

A. Orley

Respiratory System

358. Smoking and the Health of Older Men. I. Smoking and Chronic Cough

K. R. BOUCOT, D. A. COOPER, and W. WEISS. *Archives of Environmental Health* [Arch. environm. Hlth] 4, 59-72, Jan., 1962. 3 figs., 40 refs.

In the course of a research project on pulmonary neoplasia in Philadelphia 6,137 men over the age of 45 were questioned regarding their smoking habits and the presence of cough. Cough was complained of by 13% of non-smokers and 31.5% of smokers. For both smokers and non-smokers the frequency of cough increased with age. Among smokers cough increased with the amount of tobacco consumed, irrespective of whether the source was cigarettes, pipe, or cigars.

Bernard Isaacs

359. Effect of Oxygen on Patients with Pulmonary Emphysema: Changes in Minute Ventilation during Rest and after Exercise

G. J. BECK, K. NANDA, and H. A. BICKERMAN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 404-409, Feb. 10, 1962. 2 figs., 22 refs.

The authors compare the effect on the minute volume of ventilation, both during and after exercise, of inhaling air with that of inhaling oxygen in 35 patients with hypertrophic pulmonary emphysema. The patients were first seated comfortably for 20 to 30 minutes while their minute volumes of respiration were recorded on a Benedict-Roth spirometer. Then, after a 30-minute rest, they were subjected to 2-step exercise tests while inhaling 40% oxygen delivered at the rate of 8 to 32 litres per minute. When severe dyspnoea occurred the procedure was interrupted and the follow-up minute volume record was taken immediately; otherwise this was done at the completion of the exercise. The patients then repeated the experiments while breathing room air. [The original paper should be consulted for details of the patients' clinical condition and of the apparatus and technique.]

While exercising in room air the average rise in minute volume was 60% above the resting ventilation, compared with 38% when 40% oxygen was used. As would be expected, the majority of patients experienced less dyspnoea when exercising with the added oxygen. Resting tests on 15 of these patients using 100% oxygen showed an average minute volume 16.4% lower than when air was inhaled. Comparisons are made with other pulmonary function tests, and the paper concludes with a very interesting commentary on this somewhat unusual subject.

Rex Matthews

360. Oximeter Studies in Patients with Chronic Obstructive Emphysema, Awake and during Sleep

C. H. TRASK and E. M. CREE. *New England Journal of Medicine* [New Engl. J. Med.] 266, 639-642, March 29, 1962. 3 figs., 5 refs.

Remarking that sedatives should not be given at night to patients with severe emphysema because they depress ventilatory effort, the authors report a study "designed to

determine whether or not arterial oxygen saturation... may fall to a significant degree during sleep in emphysematous patients who have moderate daytime hypoxia". The 7 patients studied had daytime oxygen saturation levels of less than 96%; their CO₂ tensions were practically normal. The Waters oximeter earpiece was employed and no sedatives were given at night.

It was found that every patient showed a fall in arterial oxygen saturation during sleep, the fall being greatest in those with the lowest saturation while awake. The fall took place within a few minutes of falling asleep. There seems to be some disagreement between investigators as to whether arterial oxygen levels fall during sleep in healthy subjects, but there seems little doubt that tidal volume and minute lung ventilation fall during sleep, even in the healthy. In emphysematous subjects there is even more evidence that oxygen saturation levels are lower at night, even if they remain awake, than during the daytime.

The authors consider that there is an indication for giving oxygen at night to patients with advanced emphysema, providing carbon dioxide retention is not present.

Paul B. Woolley

361. Pseudotumoral Bronchiectasias. (Bronchiectasies pseudo-tumorales)

J. CHARPIN, E. REBOUD, H. PAYAN, and R. LIEUTAUD. *Poumon et le cœur* [Poumon] 18, 139-145, 1962. 14 figs.

The authors describe three conditions simulating neoplastic lesions which may be seen in patients with bronchiectasis and which may cause error in diagnosis. These are (1) Brock's post-tuberculous bronchostenosis of the middle lobe; (2) peribronchitic lesions with dense parenchymal collapse surrounding areas of bronchiectasis, the first anatomical description of which was by Laënnec; and (3) (the most interesting in the authors' opinion) the condition in which tumour-like radiological opacities are caused by bronchiectatic areas full of dense secretion. Such lesions are often mistaken for carcinoma, as occurred in the authors' cases, and the true diagnosis is established only on histological examination. A case of each type is described and illustrated by radiographs.

A. J. Karlish

362. Primary Lung Abscess

T. J. DUFFY and I. CHOENAS. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 269-278, March, 1962. 8 refs.

The authors have analysed all the cases of primary lung abscess, totalling 52, admitted to the Veterans Administration Hospital, Houston, Texas, between 1950 and 1960. Of the 52 patients, 34 had had some disturbance of consciousness, 19 were alcoholic, and 33 had an obvious upper respiratory focus of infection. A wide range of organisms were cultured; the combination of Gram-negative organisms and *Staphylococcus aureus* seemed to carry a poor prognosis. The usual pulmonary localization was noted, with the greatest incidence in the right upper and right lower lobes. Penicillin was given in the majority of cases, usually in

combination with other antibiotics, the average duration of administration being 48 days. Few patients were subjected to postural drainage or repeat bronchoscopy.

There were 16 deaths in the series, but only 4 were the direct result of the abscess; the remainder were due to other illnesses existing before the lung lesion developed, such as severe neurological disorders. Surgery was eventually carried out in 7 cases, and a further 6 were regarded as medical failures because of residual atelectasis or incomplete healing. In 28 patients (31 lung abscesses) medical treatment was classified as successful, and this is attributed to prolonged appropriate antibiotic therapy.

K. C. Robinson

363. Hypotension and Oliguria in Staphylococcal Pneumonia

G. KELLAWAY and H. LE GRICE. *British Medical Journal* [Brit. med. J.] 1, 426-432, Feb. 17, 1962. 3 figs., 29 refs.

At Green Lane Hospital, Auckland, New Zealand, *Staphylococcus aureus* is the commonest pathogen causing pneumonia. Thus of 132 patients admitted with pneumonia over a period of 12 months, 48 (36%) produced sputum which repeatedly gave cultures of coagulase-positive *Staph. aureus*. The mortality in this group was 25%, while the mortality in non-staphylococcal pneumonia was 10%. The authors consider that coagulase-negative staphylococci in some instances may be more pathogenic than is generally accepted, since in a group of patients with pneumonia from whom the organisms were cultured the mortality was 21%.

Of the 48 patients with staphylococcal pneumonia, 15 either presented with or later developed hypotension (systolic pressure below 95 mm. Hg) and/or significant impairment of renal function. Oliguria tended to precede or accompany the development of hypotension, but not to follow it. In this "complicated" group mortality was 67% compared with 6% in those without hypotension and renal impairment. A combination of erythromycin and novobiocin (2 g. of each daily initially) was found to be the most effective immediate treatment. In view of their experience of relapses after discontinuing antibiotic therapy the authors tend now to continue it for 4 weeks or more. Noradrenaline was the most effective hypertensive agent for the maintenance of systolic blood pressure, but in less severely affected subjects hydrocortisone and phenylephrine hydrochloride proved useful substitutes.

In some instances depression of renal function was due to acute renal tubular necrosis. Toxaemia appeared to be mainly responsible. In other instances anoxia and to a lesser extent hypotensive and hypertensive agents used in treatment seemed to be "at least contributory in causing oliguria".

T. Semple

364. Chronic Bronchitis in the Over Seventies

J. FRY. *Journal of the College of General Practitioners* [J. Coll. gen. Practit.] 5, 54-58, Feb., 1962. 1 ref.

The proportion of patients over 70 years of age with chronic bronchitis in a general practice in Beckenham, Kent, was determined, all except 8 patients out of a possible total of 454 being questioned. In these 446 patients (154 male and 292 female) two methods of diagnosis were used: (1) clinical, from the family doctor's knowledge of the patient's history, and (2) standard, from the replies to a questionnaire prepared from a previous national survey car-

ried out under the direction of the College of General Practitioners (*Brit. med. J.*, 1961, 2, 973; *Abstr. Wld Med.*, 1962, 31, 201). In these elderly patients the incidence of chronic bronchitis was higher in males than females and the rise in incidence with age was much steeper in males—from 40% in the decade 70 to 79 to 60.6% in those 80 and over, the corresponding rates in females being 26.8% and 28.1% respectively. On the other hand, the proportion of severely disabled was lower in males than females, the probable explanation, it is suggested, being that men who are severely affected die before reaching the age of 70. There was a definite relationship between smoking habits and bronchitis; in males the incidence of chronic bronchitis was more than seven times higher in smokers than non-smokers and in females it was four times higher in smokers.

P. Hugh-Jones

365. The Treatment of Exacerbations of Chronic Bronchitis in General Practice: a Comparison between Oxytetracycline and Oral Phenoxymethyl Penicillin

E. J. HOPKINS, A. M. PYE, M. SOLOMON, and S. SOLOMON. *Journal of the College of General Practitioners* [J. Coll. gen. Practit.] 5, 59-65, Feb., 1962. 9 refs.

The comparative efficacy of phenoxymethylpenicillin and oxytetracycline given by mouth in the treatment of acute exacerbations of chronic bronchitis was studied in an urban general practice in Liverpool, a double-blind technique being used. Patients with chronic bronchitis complaining of increase in cough and dyspnoea were given one of the trial tablets 4 times a day. The tablets were identical in appearance, so that neither the patient nor the doctor knew which drug was being given. The condition was classified as "mild" (the patients attending surgery), "moderate" (the patients not needing more than 2 days in bed), or "severe" (needing longer in bed). The patients were given other treatment, including antispasmodics, as required. Phenoxymethylpenicillin was given to 30 patients and oxytetracycline to 29, the age and sex ratio of the two groups being similar.

With phenoxymethylpenicillin the response was judged to be unsatisfactory in 15 patients, satisfactory in 12, and good in 3. The figures in the oxytetracycline-treated group were unsatisfactory in 11, satisfactory in 10, and good in 8. In both groups the response was best in severe cases and, by chance, there were more of them in the penicillin-treated group; it is pointed out that if allowance is made for this, the results are still more favourable in the oxytetracycline group. Moreover, the mean number of days for the patient's chest to return to normal was 5.92 (S.D. 1.49) in the oxytetracycline group (average of 13 patients) while it was 6.52 (S.D. 2.8) days in the phenoxymethylpenicillin group (average of 15 patients).

The authors conclude from the results that oxytetracycline is superior to oral penicillin in the dosage used. As regards the financial aspects of treating such exacerbations, the cost of extra visits by doctor and nurse should be assessed, in addition to the cost of drugs, when injections are given. It is considered that tetracycline or oxytetracycline in a dosage of 250 mg. 4 times a day should be administered to patients in general practice with exacerbations of chronic bronchitis, even if the attack is mild. If this fails a penicillin-streptomycin combination by injection or chloramphenicol should be given.

P. Hugh-Jones

Urogenital System

366. Oliguric Renal Failure: Evaluation and Therapy by the Intravenous Infusion of Mannitol

K. G. BARRY and J. P. MALLOY. *Journal of the American Medical Association [J. Amer. med. Ass.]* 179, 510-513, Feb. 17, 1962. 4 figs., 21 refs.

At the Walter Reed General Hospital, Washington, D.C., 24 patients with acute oliguric renal failure were treated by the intravenous infusion of mannitol. Details are given of 4 cases in which there was oliguria following postsurgical hypotension, oliguria after dehydration following prolonged vomiting and gastro-intestinal haemorrhage, or oliguria after severe abdominal injuries. Prompt mannitol therapy was successful in 16 of the 24 patients in securing and maintaining a urine flow of 60 to 100 ml. per hour. If a test dose of 12.5 g. of mannitol was followed by a urinary flow of at least 40 ml. per hour within 3 hours of administration mannitol infusion was titrated against urine output to maintain the urinary flow at approximately 100 ml. per hour. If there was no response within 3 hours of the test dose the patient was treated in the conventional manner for acute renal failure.

The mechanism by which mannitol produces its renal effect is not known, but it is suggested that since mannitol is readily filtered through the glomerulus and is not reabsorbable a high tubular concentration of mannitol is promptly attained and this tends to hold water within the tubules. It is considered that sustained mannitol diuresis is a life-saving measure in many patients with oliguria.

G. W. Csonka

367. Effect of Dietary Glucose and Protein in Acute Renal Failure

C. R. BLAGG, F. M. PARSONS, and G. A. YOUNG. *Lancet [Lancet]* 1, 608-612, March 24, 1962. 2 figs., 35 refs.

Of 163 patients referred to the Renal Research Unit at the General Infirmary at Leeds for dialysis in the treatment of acute renal failure, 13 were selected for metabolic studies since they satisfied the criteria of having oliguria and being free of complications, such as infection, which would cause the catabolic rate to fluctuate. The standard dietary regimen was 100 g. glucose daily in 500 ml. of water together with the equivalent of any sensible fluid loss, and this basic dietary regimen was compared with (1) variations of glucose intake; (2) a milk diet; and (3) a diet of milk, sugar, and eggs with the addition of an anabolic steroid. The anabolic steroid used was norethandrolone.

Glucose had a protein-sparing action, as measured by variation in urea production, that was directly related to the glucose intake—between 0 and 200 g. daily. Norethandrolone reduced protein breakdown even during starvation. With the substitution of milk for glucose, urea production increased in proportion to the nitrogen intake, but this increase could be suppressed by norethandrolone. In patients receiving norethandrolone the substitution of milk, eggs, and sugar for glucose did not significantly alter the production of urea. The effect of a protein-containing regimen on the mortality and morbidity of acute renal failure

has not yet been assessed, but it did not lead to deterioration in any case, and some patients improved in well-being while receiving the regimen.

K. G. Lowe

368. The Use of Hypertonic Saline in Patients with Renal Failure

D. A. K. BLACK and R. T. WILLIAMS. *Quarterly Journal of Medicine [Quart. J. Med.]* 31, 57-70, Jan., 1962. 14 refs.

The authors, from the Department of Medicine, Manchester University, describe the treatment of 19 cases of renal failure with hypertonic solutions of 5% saline and molar lactate. The 4 patients with extrarenal uraemia secondary to sodium depletion obtained much benefit from this treatment. Of 14 patients with chronic failure, 5 improved. One patient only went into left ventricular failure.

It is stressed that sodium depletion is difficult to recognize in renal failure, so that an empirical trial of these [apparently] harmless solutions is justified by the not infrequent striking benefits. This is especially so when there has been severe vomiting and diarrhoea, when the blood urea level suddenly rises without obvious cause, and when there is dehydration. Though isotonic solutions might be as helpful, the inability of the damaged kidney to excrete large excess volumes of water might well precipitate left ventricular failure. Illustrative cases are described in detail.

Arnold Pines

369. Protracted Glomerulonephritis in Children: with Reference to Four Anatomical Types Revealed by Renal Biopsy. (Les glomérulonephrites prolongées de l'enfant: à propos de quatre aspects anatomiques révélés par la biopsie rénale)

P. ROYER, R. HABIB, G. VERMEIL, H. MATHIEU, and M. ALIZON. *Annales de pédiatrie [Ann. Pédiat.]* 38, 793-807, March 2, 1962. 8 figs., 22 refs.

The authors have correlated the clinical and renal biopsy findings in 26 children with protracted glomerulonephritis treated at the Clinique de Pédiatrie Sociale, Paris. Four types of histological picture were distinguished which, though the authors admit that they could be stages of the same process, appear to be distinct syndromes. (1) In 3 cases there was an extra-membranous predominance of an extensive osmophilic deposit; clinically the patients had the nephrotic syndrome. (2) In another 3 cases there was gross proliferation of the wall of the glomerular capillaries or of extracapillary cells; these patients had haematuria, proteinuria, and oedema, and renal failure occurred later in 2 of them. (3) In 6 cases biopsy examination showed a lobular picture, the endocapillary cells being proliferated and separated by a hyaline substance. Here a streptococcal aetiology was considered probable, and there were steadily progressive proteinuria, haematuria, leucocytosis, and hypoproteinaemia. (4) Lastly, in 3 cases there was a proliferative extracapillary picture involving the epithelial cells; 2 were cases of the nephrotic syndrome. In the remaining 11 patients various other diseases were present. No specific therapy, including the administration of steroids, antibiotics, and chloroquine, helped any of these patients.

Arnold Pines

Endocrinology

370. A Goitre Survey in the Vale of Glamorgan

W. R. TROTTER, A. L. COCHRANE, I. T. BENJAMIN, W. E. MIAL, and D. EXLEY. *British Journal of Preventive and Social Medicine* [Brit. J. prev. soc. Med.] 16, 16-21, Jan. [received March], 1962. 7 refs.

During a chest x-ray survey of the population of the Vale of Glamorgan, South Wales, carried out by members of the Medical Research Council Pneumoconiosis Research Unit there, each subject was asked whether he or she had "ever suffered from goitre", a phrase well understood in the area, where goitre is fairly common. All those who responded in the affirmative were then examined clinically by a member of the Medical Unit of University College Hospital, London. An equal number of control subjects, selected at random from the same population and matched for age and sex with the goitre group, were also examined. Some thyroid abnormality was found in 43% of the control group. By combining the figures obtained from the goitrous subjects and from the control group it could be estimated that the over-all incidence of large simple goitres in the female population of the Vale of Glamorgan was 3.2%, the maximum incidence (8%) being found among those in the decade 55 to 64 years.

Matched pairs in which the control was also found to have some thyroid abnormality were not analysed further. However, in the remaining 181 pairs the incidence of a history of thyroid disease was much higher among close relatives of those with goitre. The explanation of this could not be deduced from the data, and there was no evidence to suggest that the susceptibility to goitre was conveyed by a recessive gene. The goitrous group were found to have spent more years of their life between birth and the development of the goitre living in the Vale than had the control subjects during the corresponding years of their lives. The results of attempts to correlate this with the source of water supply were, however, inconclusive. Estimates of the water-borne iodine intake of women with large goitres (during the period before the appearance of goitre) and of their controls failed to show a significant difference. However, inquiry about the past consumption of foods of high iodine content revealed a significant excess of persons who denied eating fish in the group with thyroid abnormality. The authors conclude that while variations in dietary habits, in so far as they affect iodine intake, are probably a factor in the causation of thyroid abnormality, there are other, unknown, influences.

H.-J. B. Galbraith

371. Autoantibodies to Thyroid Tissue Sediment Detected by the Antiglobulin Consumption Test

J. H. KITE JR., R. C. BROWN, and N. R. ROSE. *Journal of Laboratory and Clinical Medicine* [J. Lab. clin. Med.] 59, 179-194, Feb., 1962. 2 figs., 24 refs.

Serological reactions with insoluble tissue antigens may be of considerable importance in the investigation of autoantibodies, but their demonstration can present technical difficulties. The complement fixation test, for instance, is complicated by the anticomplementary action of tissue par-

ticles. The "antiglobulin consumption test" offers a quantitative technique for the demonstration of specific antibody-insoluble tissue antigen reactions. It has been used to detect autoantibodies reacting with connective tissue and heart, liver, brain, and other tissues. The test is performed as follows. Washed tissue is incubated with (1) test serum and (2) control serum. If the test serum contains specific antibodies to an insoluble cellular antigen these will remain attached to the tissue when the serum is removed by washing. Such an antibody has been shown to be a γ globulin and its presence is detected by its power of "consuming" antiglobulin serum. Antiglobulin serum is therefore added to the treated tissue, removed, and serially diluted. Its titre of antiglobulin is then determined as in the usual Coombs test with sensitized erythrocytes, when the titre should be lower in the test serum than in the control serum if antibody was present in the former.

Working at the University of Buffalo School of Medicine, New York, the authors have investigated several modifications of the original technique described by Steffen in 1954 in an attempt to devise a standard test for the detection and measurement of autoantibodies to thyroid tissue sediment. Human thyroid glands obtained at necropsy or operation were ground with buffered saline, centrifuged, and washed 15 times, when the supernatant fluid was shown to be free from detectable thyroglobulin and serum. The sediment was suspended in distilled water, and used as antigen in the test. [The method of preparation of antiglobulin serum is fully described, but for this and also for exact details of quantities, times, and temperatures in performing the test the original paper must be consulted.]

The antigen is incubated first with inactivated patient's serum and then with control serum, undiluted or in serial dilutions, at 37° C. for 10 minutes. The tissue sediment is then washed 8 times with saline, treated with Coombs serum (anti-human-euglobulin rabbit's serum), centrifuged, and the supernatant fluid removed. Serial dilutions of this supernatant fluid are then prepared, sensitized erythrocytes added, and the degree of agglutination determined macroscopically. A positive reaction is seen in a lower titre in the test row of tubes compared with the control row. By carrying out tests with human liver, spleen, and kidney tissue sediments the authors showed that the test is specific for thyroid tissue sediment. Studies of its specificity were also made by absorption tests; thus absorption of a positive serum with thyroid sediment removed its ability to show the consumption reaction. The possibility that a positive result was due to increased absorption by the sediment of non-specific globulin, because the test serum had a high globulin level, was also investigated. The test was performed with sera from 19 patients, all showing elevated globulin levels and including some with lupus erythematosus. In only 2 of these sera was the test positive, and then only in very minor degree. Experiments indicated that one of the antibodies participating in the antiglobulin consumption test is the antithyroglobulin antibody. Positive reactions were obtained with 23 of 64 sera from patients with thyroiditis. Nearly all positive sera had elevated haemagglutina-

tion titres, a direct correlation being observed in most instances. No correlation, however, was found between the results of the test and those of the complement fixation test.

Kenneth Stone

372. Hyperparathyroidism: Analysis of Recent Experiences, Clinical Spectrum, and Diagnostic Tests

F. A. RIDDICK JR. and E. REISS. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 183-197, Feb., 1962. 13 figs., bibliography.

The authors have analysed the details of 34 consecutive cases of primary hyperparathyroidism seen at Barnes Hospital, St. Louis, Missouri, during the years 1956-60. In 24 cases the clinical diagnosis had been confirmed by histological examination. In 4 cases parathyroid adenomata were found while the neck was being explored because of thyroid disease. In 6 cases, although there was clinical and laboratory evidence characteristic of primary hyperparathyroidism, pathological confirmation was not yet available. Bone disease was present in 7 cases, and 3 of these had generalized osteitis fibrosa cystica. Of 18 patients with renal involvement, 3 had nephrocalcinosis. There was one case with acute pancreatitis and 2 cases of multiple endocrinopathy.

Hypercalcaemia was present at some time in all cases but one, though it was noted that there was considerable fluctuation in the serum calcium level. Excluding the cases with renal insufficiency and 2 others, all patients had hypophosphataemia at least once. Alkaline phosphatase estimation showed a significantly raised level in 27 cases. The tubular reabsorption of phosphate was low in 23 of the 24 patients studied. The importance of preventing phosphate depletion before tubular reabsorption of phosphate is estimated is emphasized.

There was a single parathyroid adenoma in 19 cases; 4 cases had multiple adenomata, and one had chief-cell hyperplasia.

Charles Rolland

373. Genetic and Constitutional Aspects of Diabetes Mellitus. [Monograph, in English]

S. E. NILSSON. *Acta medica Scandinavica* [Acta med. scand.] 171, Suppl. 375, 1-96, 1962. 10 figs., bibliography.

374. Diabetic Retinopathy

J. M. B. BLOODWORTH JR. *Diabetes* [Diabetes] 11, 1-22, Jan.-Feb., 1962. 33 figs., bibliography.

In the past 5 years at the Ohio State University Hospital, Columbus, post-mortem examination has included removal of the eye, approximately 300 eyes having been thus removed from 160 diabetic patients. Histological examination of this material has suggested that the emphasis hitherto placed on capillary changes has been too great. There is no sure evidence that the capillary changes initiate the process; in fact, the present studies indicate that degenerative changes in the nervous elements of the retina may precede the vascular changes. Associated with degeneration of the neurones are oedema of the plexiform layers, development of "cotton-wool" exudates in the nerve-fibre layer, and atrophy of the nerve-fibre layer and optic nerve.

Observations on microaneurysms, haemorrhages, exudates, and capillary proliferation are described and discussed in detail. From these observations the author presents a hypothesis for the development of diabetic retinopathy. It

is regarded as a complex degenerative disease of all elements of the retina. Breakdown products of cells accumulate in the plexiform layers as waxy exudates. Loss of support from the nervous elements and splitting of the capillary wall lead to the formation of microaneurysms. The final picture of advanced diabetic retinopathy is a combination of degeneration of nervous elements with secondary gliosis, microaneurysmal degeneration of capillaries, neovascularization, exudates, cystoid degeneration, and haemorrhages.

K. O. Black

375. Retinopathy and Neuropathy in One Hundred Growth-onset Diabetic Patients

R. T. COLLYER and B. E. HAZLETT. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 85, 1328-1334, Dec. 16, 1961. 9 figs., 27 refs.

An out-patient clinic for follow-up care and investigation of patients with diabetes mellitus of onset before the age of 16 was established at the Toronto General Hospital in 1948, and the present report concerns 100 patients examined at this clinic between 1958 and 1960. A family history of diabetes was found in 58 of the 100 patients.

The incidence of retinopathy was related to duration of diabetes, and was seen in some degree in all cases in which the duration exceeded 20 years. The patients with retinopathy consisted of a large group with minor changes and a much smaller group showing severe damage. It is suggested that the appearance of extensive patches of exudate and/or numerous haemorrhages marks the potential case of retinitis proliferans, and that it may be more fruitful to study this change than the first appearance of microaneurysms. Good diabetic control did not prevent retinopathy, but was a factor in preventing severe retinopathy and blindness. Severe diabetic neuropathy was apparently more influenced by the degree of biochemical control of the diabetes than by the duration of the disease, while minor degrees of neuropathy were more closely related to duration of the diabetes.

K. O. Black

376. A Clinical and Laboratory Study of Insulin Dosage in Diabetic Acidosis: Comparison with Small and Large Doses

C. E. SHAW JR., G. E. HURWITZ, M. SCHMUKLER, S. H. BRAGER, and S. P. BESSMAN. *Diabetes* [Diabetes] 11, 23-30, Jan.-Feb., 1962. 2 figs., 19 refs.

Thirty cases of diabetic acidosis were studied and treated during the first 8 hours after hospitalization [at University Hospital, Baltimore, Maryland] according to a standardized program which varied only in insulin dosage. By random selection, each patient was given either small insulin dosage of 65 to 180 units (average 124 units) or large dosage of 200 to 825 units (average 387 units) during the first 8 hours of therapy. The following tests were performed on each patient at the time of admission and the 4th and 8th hours after instituting treatment: blood glucose, plasma CO_2 -combining power, quantitative blood beta-hydroxybutyric acid and total blood ketones, blood urea nitrogen and serum sodium, potassium, chloride and phosphorus. Clinical and chemical improvement was equally satisfactory in both groups at the end of 8 hours of therapy. This study suggests that there may be a limit to the amount of insulin which can effectively re-establish carbohydrate metabolism and reduce ketonemia during the first 8 hours of therapy of diabetic acidosis and that larger insulin doses may not exert greater therapeutic effect.—[Authors' summary.]

The Rheumatic Diseases

377. **The Immune Adherence Phenomenon in the Diagnosis of Acute Rheumatism.** (Toepassing van de immuun-adherentie ("immune adherence") bij de diagnostiek van acuut reuma)

M. R. H. STOPPELMAN. *Nederlands tijdschrift voor geneeskunde* [Ned. T. Geneesk.] 106, 112-115, Jan. 20, 1962. 9 refs.

The feasibility of using the immune adherence phenomenon described by Nelson (*Science*, 1953, 118, 733) for the serological diagnosis of acute rheumatic fever in children was investigated at the Children's Hospital, University of Amsterdam. The titre of adherence factor against haemolytic streptococci Group A was determined in sera from 1,429 children, of whom 129 had rheumatic fever of recent onset, 80 had acute haemolytic streptococcal infections, and the remaining 1,220 served as controls.

In the acute rheumatic fever group sera from 4 children aged from 3 to 5 years had titres of 512, 256, 128, and 16 respectively, 25 specimens of sera from children aged 5 to 7 years had titres ranging from 512 to 8, the titre being 256 in 9 cases and 128 in 6, while in 22 specimens of sera from children aged 7 to 9 years the titres ranged from 2,048 to 16, being 256 in 8 cases and 2,048 in one. In the 9 to 11 age group 32 sera showed titres ranging from 16 to 256, while in 46 sera from children aged 11 years and older the range was from 64 to 2,048 and here the numbers were evenly distributed throughout. In the group with streptococcal infections (in which the same age groups were studied) the titres ranged from less than 8 to 1,024, the greatest proportion being 64 or lower. In the control series titres of 8 and 16 occurred most frequently. In general there was considerable overlapping of all groups, and the mean adherence titres increased with the age of the patient.

The antistreptolysin titre and adherence titre were determined at the same time in sera from 81 children with acute rheumatism and 50 control children with other diseases. Of the former group, 62 showed adherence titres of 128 or higher and 63 had an antistreptolysin titre of 250 units per ml., whereas in the control group only 2 and 15 had these titres respectively. The adherence titre was also measured before and after adding extra complement to sera from patients in the three groups previously studied, but the difference was too small to allow any conclusions to be drawn. It is concluded that although an adherence titre is obtainable in healthy subjects and patients with diseases other than acute rheumatic fever, the titres are usually higher in the latter disease. This test, which can be performed in any bacteriological laboratory, has therefore a certain value in the diagnosis of acute rheumatic fever.

Anne Tothill

378. **The Preceding Illness of Acute Rheumatic Fever**

J. G. ZAGALA and A. R. FEINSTEIN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 863-866, March 17, 1962. 13 refs.

The presence or absence of preceding pharyngeal symptoms was correlated with certain clinical features of the first attacks of acute rheumatic fever in 183 children and adol-

escents. A preceding sore throat had occurred in 46%, nonspecific respiratory symptoms without sore throat had been present in 21%, and 33% of the patients had had no symptoms before the attack. The presence or absence of pharyngeal symptoms bore no significant relation to the sex or age of the patients, to their initial cardiac status, or to the appearance of arthritis as a presenting complaint. In patients with symptomatic sore throats, a majority (79%) had been untreated, and the remainder received therapy inadequate to eradicate Group A streptococci. The inadequate treatment for these illnesses did not seem to affect or prevent subsequent cardiac damage. The sore throat occurred within 1 to 3 weeks before the onset of rheumatic fever in 51 (61%) of the 84 patients who had had sore throats. In 15% of these patients it occurred simultaneously with the onset of rheumatic fever, and in 15% it came more than 4 weeks before the onset of rheumatic fever.

These data indicate that a sore throat frequently fails to appear as an antecedent warning of rheumatic fever, that it is often inadequately treated when present, and that its rheumatic sequel may occur earlier or later than the classically-described 2-week incubation interval. The "gestation" period of the streptococcal infection, its eruption or failure of eruption into clinical symptoms, and the eventual appearance of rheumatic fever follow different patterns and intervals for each patient.

The prevention of first attacks of rheumatic fever requires that physicians and the public be more aware of the need for identification and adequate treatment of streptococcal pharyngitis, although these measures alone will still fail to prevent rheumatic fever in the more than 50% of patients who are not identified because they do not develop sore throats.—[Authors' summary.]

379. **Phagocytosis of Urate Crystals in Gouty Synovial Fluid**

D. J. MCCARTY JR. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 288-295, March, 1962. 5 figs., 13 refs.

The author of this paper from Hahnemann Medical College and Hospital, Philadelphia, states that, as every patient whose synovial fluid contained urate crystals was eventually proved to have gout, this finding has come to be regarded as pathognomonic of the disease. Not all crystals, however, floated freely in the fluid, but some appeared to be intracellular, and he now enlarges upon this observation. By means of a polariscopic technique using a $\times 12.5$ ocular and a $\times 100$ oil-immersion objective to examine wet preparations stained supravitaly with neutral red he has demonstrated phagocytosis of urate crystals by polymorphonuclear leucocytes and monocytes, but not by lymphocytes. Urate crystals were observed in synovial fluid at all stages from 12 hours to 8 weeks after an acute attack of gout. Continued observation of the wet preparations showed initial phagocytosis followed by some uricolysis of the crystal as it is ingested by the myeloperoxidase of the leucocytes, with a simultaneous disintegration of the leucocyte,

which may eventually extrude the remaining crystal to be re-phagocytized by another leucocyte. Colchicine in varying near-physiological amounts failed to inhibit the crystal phagocytosis. Suggestions are put forward to explain a possible mechanism by which tophi are formed.

Harry Coke

380. Treatment of Localized Forms of Scleroderma

C. J. D. ZARAFONETIS. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 147-158, Feb., 1962. 7 figs., 15 refs.

The author has administered potassium *p*-aminobenzoate ("potaba") to 14 selected patients with localized scleroderma. In all cases sclerosis was diminished. Atrophy secondary to sclerosis and pigmentation were less affected. The author considers that this improvement was greater than would have been expected spontaneously in a control series. He suggests that the sclerosis might be due to an imbalance between the local liberation and degradation of serotonin and that potassium *p*-aminobenzoate might act by favouring the breakdown of serotonin. G. L. Asherson

RHEUMATOID ARTHRITIS

381. Pericarditis in Still's Disease. (La péricardite de la maladie de Still)

P. MOZZICONACCI and F. HAYEM. *Revue du rhumatisme et des maladies ostéo-articulaires* [Rev. Rhum.] 29, 1-11, Jan.-Feb. [received April], 1962. 10 figs., 19 refs.

From the Hôpital Bictre, Paris, the authors describe 7 cases of pericarditis complicating the course of Still's disease. In 3 cases an effusion was observed clinically and radiologically. In one of these the pericarditis occurred during the first attack of the disease, but in later attacks it did not recur and left no sequelae. In the second case it occurred during a relapse and in the third during the terminal phase of the disease. In this last case the pericarditis was confirmed post mortem and no Aschoff bodies were found histologically.

The characteristic changes in the electrocardiogram (ECG) are found in the T wave and ST segment. There may be flattening, inversion, or peaking of the T wave, particularly in standard Leads II and III and in the precordial leads AV4 to AV6; the ST segment may be elevated in these leads. These changes are always transitory and this helps to exclude myocardial involvement. The ECG showed characteristic changes in the first 3 cases and in a further group of 4 cases (studied at various other Paris hospitals) these ECG changes were the only definite evidence of involvement of the pericardium. In the first case in this group a negative T wave in Lead I with elevation of ST segment in Lead III was noted at the beginning of the disease, the ECG pattern reverting to normal within 3 months. In the second case the characteristic changes were observed during a relapse, in the third during a period of cardiac failure, and in the fourth during a particularly severe phase in the evolution of the disease. The authors distinguish Still's disease from other forms of chronic polyarthritis in children. Thus the 7 cases of pericarditis described occurred among 21 cases of Still's disease, whereas there was no instance of pericarditis among 8 cases of juvenile chronic polyarthritis observed over the same period. William Hughes

382. Rheumatoid Factors in Patients with Silicosis with Round Nodular Fibrosis of the Lung in the Absence of Rheumatoid Arthritis. With a Note on the Failure to Induce Such Factors in Animals

W. SCHROEDER, E. C. FRANKLIN, and C. McEWEN. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 10-18, Feb., 1962. 42 refs.

At the New York University College of Medicine serum was examined from 10 selected coal-miner patients who had pulmonary lesions of the Caplan type, but with no evidence of arthritis, other collagen disease, or liver disease. The patients ranged in age from 48 to 63 years and had been exposed to coal dust for 12 to 33 years. Repeated examinations for tubercle bacilli were negative. All 10 sera gave positive reactions in the agglutination-inhibition test of Ziff *et al.* (Amer. J. Med., 1956, 20, 500; Abstr. Wld Med., 1956, 20, 387), 8 gave positive agglutination of sensitized sheep cells with the euglobulin fraction, and again 8 gave positive results in the latex fixation test of Singer and Plotz (Amer. J. Med., 1956, 21, 888; Abstr. Wld Med., 1957, 22, 50) and the capillary latex test of Tanner and Ziff (Arthr. and Rheum., 1958, 1, 376). Five sera were shown to have elevated γ -globulin levels by the zinc turbidity method. Four sera were examined in an analytical ultracentrifuge; they contained macroglobulins having the typical 19-S sedimentation constant, but in only one case was there a detectable amount of 22-S material. The macroglobulins were shown to be dissociable with 2:mercaptoethanol.

In a further experiment 107 male guinea-pigs and 44 male rats were injected in various ways with suspensions of quartz dust. Examinations for agglutinating properties were made by the serological methods recorded above from 6 to 38 weeks later and all results proved entirely negative, though many animals had gross evidence of silicotic nodules. The significance of these findings is discussed and it is considered that they "offer strong evidence against the hypothesis that silica in the form employed [and administered by the methods employed] is responsible for the production of positive rheumatoid factor tests". Harry Coke

383. Methylprednisolone Acetate in Intra-articular Therapy: Clinical, Biochemical, and Chromatographic Studies

W. R. MURDOCH and G. WILL. *British Medical Journal* [Brit. med. J.] 1, 604-606, March 3, 1962. 2 figs., 23 refs.

At Glasgow Royal Infirmary intra-articular injections of 40 mg. of methylprednisolone acetate were given into the knee-joints of 48 patients suffering from rheumatoid arthritis. In all, 69 joints were so treated, the injections varying in number from 1 to 6 being given at weekly intervals until complete relief of pain and swelling occurred; a small amount of synovial fluid (3 to 5 ml.) was removed for routine analysis. Relief of pain started within 6 hours of the injection and became complete in 24 hours. In more than half the patients only 2 injections were required to produce resolution of the effusion and none failed to get relief of pain and effusion. At the end of a follow-up period ranging from 10 to 30 months 49 joints were still in remission.

Examination of the specimens of synovial fluid obtained from 52 joints during the course of the treatment showed that there was a fall in the total cell count in all cases, and that the total protein content of the fluid fell in 48 cases. Electrophoresis was carried out on the fluid from 40 joints. During treatment the albumin content of 30 fluids from

joints showed a rise, 6 were unchanged, and 4 showed a small fall, while detailed analysis of the globulin fractions showed a tendency for all of these fractions to diminish. To determine the persistence of methylprednisolone acetate within the joint cavity a separate study was made on 40 joints which were aspirated at intervals of 7 to 21 days after the injection of 40 mg. of the drug, chromatograms being prepared from the specimens. The steroid present was identified by (1) absorption of ultraviolet light of wave length 253 m μ , (2) reduction of blue tetrazolium reagent, and (3) the position on the chromatogram in relation to the markers. The results showed that the steroid could be detected in the joint as long as 21 days after an injection. The authors point out that the results are very similar to those they obtained in their earlier investigation of prednisolone trimethylacetate (*Brit. med. J.*, 1959, 1, 1267 and 1271; *Abstr. Wld Med.*, 1959, 26, 374), but the chromatographic studies of persistence of the steroid favour methylprednisolone.

C. E. Quin

384. A Critical Evaluation of the Diagnostic Features of the Feet in Rheumatoid Arthritis

J. J. CALABRO. *Arthritis and Rheumatism* [*Arthr. and Rheum.*] 5, 19-29, Feb., 1962. 6 figs., 37 refs.

In the hope that it may arouse more interest in an area often neglected, the clinical and radiographic manifestations of rheumatoid arthritis in the feet have been presented. Clinical features consist of: (1) progressive hallux valgus, often associated with bunion at the first metatarsal head; (2) bilateral and symmetrical hammer toes or cock-up toes, usually with superimposed corns; (3) metatarsal head depression, spread (spread-foot), and tenderness; (4) pes planovalgus; and (5) painful heels. X-ray characteristics include achillobursitis, peritendinitis, and metatarsal head and calcaneal erosive lesions which may proceed through stages of rarefaction, erosions, remineralization, and spur formation. Though none of these features singly renders a diagnosis of rheumatoid arthritis, their presence together may often aid considerably in the differential diagnosis of arthritis. The rheumatoid foot features are discussed in the light of other causes and the possible mechanisms and factors responsible for these changes.—[Author's summary.]

385. Chloroquine and Hydroxychloroquine Therapy in Rheumatoid Arthritis

E. SCULL. *Arthritis and Rheumatism* [*Arthr. and Rheum.*] 5, 30-36, Feb., 1962. 7 refs.

This paper from Hartford Hospital, Hartford, Connecticut, assesses the therapeutic value of antimalarials in 160 patients with rheumatoid arthritis, with 36 patients given a placebo serving as controls. In one group 80 patients not responding satisfactorily to corticosteroid and salicylate therapy were given chloroquine, usually 250 mg. in a single daily dose, for an average period of 24.2 months. In a second group 80 patients, of whom 59 had previously received corticosteroids and salicylates and 21 salicylates alone, were given hydroxychloroquine, 200 mg. twice daily for an average period of 17.7 months. Of the 36 control patients in the third group, given a placebo, 30 had previously received corticosteroids and salicylates, while 6 had had salicylates only. Each patient was classified at the outset and at the end of the therapeutic trial into one of the disease Stages I to IV according to the criteria of the Ameri-

can Rheumatism Association. Comparisons of grades of response obtained and functional impairment were made also using the criteria of the American Rheumatism Association.

An analysis of the clinical responses (full gradings given in tabular form) showed that the patients receiving chloroquine or hydroxychloroquine were significantly improved ($P > 0.001$). Of the 80 patients receiving chloroquine and corticosteroids, it was possible to reduce the dosage of corticosteroids in 44 (55%) and discontinue them altogether in 11 (14%). Of the 59 patients receiving corticosteroids and hydroxychloroquine, corticosteroids could be reduced in 35 (59%) and discontinued in 10 (17%).

Side-effects with chloroquine included gastro-intestinal disturbances (6 patients), weight loss (6), rashes (3), and depigmentation of hair (4). Those with hydroxychloroquine included rashes (2), gastro-intestinal upsets (2), vertigo (2), and loss of weight (1). Treatment was discontinued because of side-effects in 17 cases (11%).

Exacerbations or relapses were observed in treated and control groups in approximately equal numbers—chloroquine group 11%, hydroxychloroquine group 10%, and control group 8.3%.

The author concludes that chloroquine and hydroxychloroquine possess definite antirheumatic activity.

Hewett A. Ellis

386. Preliminary Study of the Results Obtained with Various Corticoids and Combinations of Corticoids in 145 Cases of Rheumatoid Arthritis. (Étude préliminaire sur les résultats obtenus avec divers corticoïdes et leur association dans 145 cas de polyarthrite rhumatoïde)

J. CAYLA, A. GUÉRARD DES LAURIERS, and F. COSTE. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] 38, 670-676, Feb. 26, 1962.

In this study of the value of the newer corticosteroids carried out at the Hôpital Cochin, Paris, 94 cases of rheumatoid arthritis already under treatment with steroids were given a different steroid and observed for changes in control of the disease and for side-effects, while a further 55 cases were treated with a combination of two steroids.

Of 33 patients previously receiving prednisone or prednisolone and then changed to equivalent doses of dexamethasone, 11 were "better" and 14 "worse"; side-effects were numerous, the most common being "cushingoid" signs and vertebral collapse. Of 25 patients also receiving prednisone or prednisolone in whom this was replaced by equivalent doses of triamcinolone, 13 were better, and 6 worse; side-effects, again numerous, were however of a different type, consisting mainly of digestive disturbances and weakness and wasting of the muscles of the limbs. Of 14 cases changed from prednisone or prednisolone to methylprednisolone, 7 were better and 5 were worse; side-effects were here less severe and only one patient had to discontinue the drug.

By the use of various combinations of two of the above drugs it was found possible to reduce, but not entirely to eliminate, the incidence of side-effects. The authors were not able to discover a combination of these drugs that was outstandingly successful, but they conclude that a mixture of triamcinolone with prednisolone or dexamethasone, preferably in a proportion of 1:2, often proved the most efficacious.

B. E. W. Mace

Neurology and Neurosurgery

387. **Clinical and Electroencephalographic Studies in Atrophic Brain Diseases.** (Клинические и электроэнцефалографические исследования при атрофических заболеваниях мозга)

Е. Я. ŠTERNBERG and G. M. FRENKEL'. *Журнал Невропатологии и Психиатрии* [Zh. Nevropat. Psikhlat.] 62, 114-124, No. 1, 1962. 5 figs., 24 refs.

The authors review the literature on atrophic diseases of the brain and point out that in contrast to Alzheimer's disease there are only isolated reports of the changes in the electroencephalogram (EEG) in Pick's disease. The present paper concerns the EEG findings in 22 cases of Pick's disease and 26 cases of Alzheimer's disease which were studied at the Research Institute of Psychiatry, Moscow, between 1958 and 1960. In all the 23 cases which came to necropsy the clinical diagnosis was confirmed.

In Alzheimer's disease the EEG showed a predominant irregular rhythm at 4 to 6 per second with an amplitude of 40 to 60 μ V. on which were superimposed polymorphous slow waves at 1.5 to 3 per second and 70 to 100 μ V. There was a levelling out of differences in leads from different regions of the brain. The usual response of the EEG to rhythmic light and sound stimuli was absent. On the EEG of only one out of 6 patients suffering from epileptic fits were any epileptic complexes registered, and these complexes became progressively less evident despite an increase in the frequency of the fits. In addition to the generalized abnormalities local changes in the form of sharp waves or slow waves of higher amplitude were sometimes seen.

The EEG changes in Pick's disease were less uniform. Most frequent was the presence of an alpha rhythm of low or medium amplitude and levelling out of the regional differences in the various leads. Sometimes there were isolated slow waves and spikes of medium voltage. Often the EEG could be considered as being on the borderline of normal despite clinical evidence of pronounced focal and general impairment. Some cases showed a preponderance of generalized slow activity at 5 to 6 per second and the changes resembled those seen in Alzheimer's disease. In all cases of Pick's disease the EEG showed a corresponding response to rhythmic light and sound stimuli. Three typical case histories are presented in detail.

The authors suggest that the contrasting EEG findings are a useful additional point in the differential diagnosis of the two diseases. They relate the EEG changes to the peculiarities of the respective pathological processes and in particular ascribe the less severe changes in the EEG in Pick's disease to the more localized involvement of phylogenetically young parts of the brain. G. P. McGovern

388. **Electroencephalographic Study of Patients with Acute Aseptic Meningitis**

F. A. GIBBS, E. L. GIBBS, P. R. CARPENTER, and H. W. SPIES. *Pediatrics* [Pediatrics] 29, 181-186, Feb., 1962. 3 figs., 15 refs.

From the Municipal Hospital for Contagious Diseases, Chicago, the authors report the electroencephalographic (EEG) findings in 158 patients suffering from acute aseptic

meningitis. EEG abnormalities were found in 33% of the series and were more common in children. The recordings returned to normal within 10 days in all but 2 cases, one of which continued to show theta activity while in the other, 3 weeks after clinical recovery, 6-c.p.s. positive spike discharges replaced the slow activity which was present during the acute phase; in this case further improvement took place 5 weeks later. The incidence of EEG abnormalities was slightly higher in cases in which the infecting agent was not identified than in those in which E.C.H.O. or Coxsackie viruses were isolated. The numbers of patients with poliomyelitis or mumps viruses were too small to allow of any reliable estimate of the occurrence of EEG abnormalities in these groups.

H. S. Schutta

389. **Effect of Intrathecal Purified Protein Derivative of Tuberculin in Multiple Sclerosis**

J. COLOVER, M. KREMER, R. E. LOVELACE, and J. R. SILVER. *Journal of Neurology, Neurosurgery and Psychiatry* [J. Neurol. Neurosurg. Psychiat.] 25, 79-85, Feb., 1962. 16 refs.

In 1957 Smith *et al.* suggested (*J. Neurol. Neurosurg. Psychiat.*, 20, 1; *Abstr. Wld Med.*, 1957, 22, 138) that intrathecal administration of purified protein derivative (P.P.D.) might be beneficial in patients with disseminated sclerosis. The present authors describe a clinical trial of such injections in 36 patients with disseminated sclerosis at the Middlesex Hospital, London. The patients selected were deteriorating or had recently had fresh relapses. Those giving a negative response to the Mantoux test were vaccinated with B.C.G. and a small number with extreme skin sensitivity to P.P.D. were desensitized. From 1 to 6 intrathecal injections were given and ACTH was administered intramuscularly to mitigate the severe reactions. No evidence of any favourable results was obtained; in fact, most of the patients deteriorated and there was a high relapse rate which may have been related to the injections.

R. Wyburn-Mason

390. **The Late Onset Myopathy: a Clinicopathologic Study of 131 Patients.** [In English]

G. M. SHY. *World Neurology* [Wld Neurol.] 3, 149-160, Feb. [received April], 1962. 9 figs., 14 refs.

The author, working at the National Institutes of Health, Bethesda, Maryland, has studied 131 patients in whom the clinical picture of myopathy appeared after the age of 30. All had been subjected to muscle biopsy, electromyography, and various laboratory investigations. Unequivocal evidence of collagenosis, including scleroderma, dermatomyositis, polyarteritis nodosa, rheumatoid arthritis, disseminated lupus erythematosus, and Sjögren's syndrome, was stated to have been present in 65 patients, and 6 had sarcoidosis. Underlying carcinoma was eventually discovered in 24, of whom 20 were over the age of 50. It is suggested that the term "polymyositis" should be used only when the myopathy is determined by bacterial, viral, or parasitic invasion, of which there were no examples in this series.

The author holds the view that polymyositis is not an entity, but is caused by a wide variety of pathological pro-

cesses, many of which belong to the collagen group of diseases. In his own series of 131 cases, however, he was unable to ascribe any cause in no fewer than 36.

Hugh Garland

391. Myasthenia Gravis and the Thyroid Gland

D. B. DRACHMAN. *New England Journal of Medicine* [New Engl. J. Med.] 266, 330-333, Feb., 15, 1962. 2 figs., 13 refs.

The effect of the metabolic status on the weakness of a myasthenic patient was studied at the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland, in a woman, aged 45, who suffered from myasthenia gravis and thyrotoxicosis and who had been subjected to total thyroidectomy. After operation the course of the myasthenia was studied when the patient was made hypothyroid by withdrawal of thyroid medication, when she became euthyroid following administration of 100 to 150 μ g. [?] daily of triiodothyronine, and when she became hyperthyroid on the dosage of this drug being increased to 600 μ g. The myasthenia was aggravated when the patient was either hypothyroid or hyperthyroid; when she was euthyroid muscle weakness was considerably less. Repeated tests with edrophonium chloride demonstrated that the weakness was due to myasthenia gravis and was not a direct muscular effect of hyperthyroidism or hypothyroidism.

J. W. Aldren Turner

392. A Myasthenic Syndrome Associated with Bronchial Carcinoma

R. P. WISE and V. MACDERMOT. *Journal of Neurology, Neurosurgery and Psychiatry* [J. Neurol. Neurosurg. Psychiat.] 25, 31-39, Feb., 1962. 4 figs., 39 refs.

The authors of this paper from St. Thomas's Hospital, London, report a study of 3 patients with carcinoma of the bronchus who exhibited a "myasthenic syndrome" similar to that previously described by Eaton and Lambert (*J. Amer. med. Ass.*, 1957, 163, 1117). This condition differs from myasthenia gravis in several respects. Weakness and easy fatigability of muscles, especially those of the pelvic girdle, are present and there is marked sensitivity to tubocurarine, but tendon reflexes are impaired and the response to neostigmine, particularly when given by mouth, is poor. Aching pains in the muscles are frequent, but involvement of ocular and bulbar muscles apparently does not occur. The electromyogram shows a pattern of low-voltage, short-duration potentials with no evidence of denervation. Histological examination in 2 cases revealed a non-specific degenerative process affecting the distal nerves and motor end-plates, unlike that usually seen in myasthenia gravis.

J. W. Aldren Turner

393. Peripheral Nerve Conduction in Diabetic Neuropathy

R. W. GILLIATT and R. G. WILLISON. *Journal of Neurology, Neurosurgery and Psychiatry* [J. Neurol. Neurosurg. Psychiat.] 25, 11-18, Feb., 1962. 5 figs., 15 refs.

A study of motor conduction velocity and nerve action potentials in patients with diabetic neuropathy is reported from the Middlesex Hospital and the National Hospital, Queen Square, London. The authors examined 5 patients with a predominantly sensory neuropathy affecting the legs, none of whom had muscle wasting or weakness. Velocity was estimated in the motor fibres to the extensor digitorum brevis and nerve action potentials in the anterior tibial nerve.

The major abnormality found was absence of nerve action potentials in 4 patients and a very small potential in one; motor velocity was less constantly affected. In 2 further patients with a mixed motor and sensory neuropathy conduction velocity in the lateral popliteal nerve was substantially reduced. A group of 5 diabetic patients with isolated peripheral nerve lesions were also examined—2 with ulnar nerve lesions, 2 with median nerve lesions, and one with lateral popliteal nerve involvement. Electrical studies on clinically unaffected nerves showed that values were within the normal range, while in the affected nerves there were abnormalities in either motor velocity or nerve action potentials in every case. The authors consider that in isolated peripheral nerve lesions in diabetic patients mechanical factors are often of considerable importance.

J. W. Aldren Turner

BRAIN AND MENINGES

394. Long-range Results in the Treatment of Intractable Pain by Stereotaxic Midbrain Surgery

H. T. WYDIS and E. A. SPIEGEL. *Journal of Neurosurgery* [J. Neurosurg.] 19, 101-107, Feb., 1962. 15 refs.

The long-term results in 54 patients treated for relief of pain by stereotaxic midbrain surgery are discussed in this paper from Temple University Medical Center, Philadelphia. The operation was designed to produce lesions in the spinothalamic and quintothalamic tracts at the upper midbrain level, together with adjoining areas of the tegmentum dorsal to the red nucleus. When pain was associated with particularly pronounced emotional reactions the mesencephalotomy was combined with the production of a further lesion in the dorso-medial nuclei of the thalamus. The patients were all suffering from severe pain unrelieved by medical (and in some cases by surgical) treatment, and included examples of postherpetic pain, atypical facial pain, tabes dorsalis, pain from malignant disease and amputation neuroma, and central pain.

Immediate relief of pain was obtained in 39 patients, but this number later fell with the passage of time to a total of 17 with complete or partial permanent relief. Eleven patients obtained no relief from the operation, and 4 patients died; 2 of the latter were suffering from vascular hypertension and 2 from neoplastic disease. Complications included persistent and disturbing dysaesthesiae after the operation in 2 patients, and motor disturbances of face and eyes and ataxia with intention tremor were noted, together with occasional minor complications.

The authors do not claim that mesencephalotomy is the final answer to the problem of surgical treatment of pain, but they regard it as a refined method of producing a lesion in the spinothalamic and quintothalamic tracts and adjacent pain-conducting systems which has advantages over mesencephalic tractotomy.

J. B. Stanton

395. The Influence of Thyroid on Water Metabolism in Migraine

K. M. HAY. *Journal of the College of General Practitioners* [J. Coll. gen. Practit.] 5, 86-106, Feb., 1962. 9 figs., 27 refs.

Patients subject to frequent attacks of migraine have a constitutional instability of their salt and water balances, with retention occurring in the prodromal phase, and a diuresis during and after the onset of the main symptoms.

These changes do not in themselves account for migraine, but they serve as indicators of the state of flux in the background metabolism, which is part of the migraine syndrome.

Evidence has been given to show that small doses of thyroid can modify the diurnal weight changes in migraine, with clinical improvement in the majority of cases. Thyroid deficiency in migraine is functional and fleeting in nature, and not an organically based condition. There is reason to believe that it is due to failure of stimulation of the thyroid gland through the hypothalamic pituitary pathway following previous excessive or prolonged stimulation. It is suggested that the fluid and salt retention is due to release of the A.C. T.H. mechanism after temporary T.S.H. insufficiency, and that migraine occurs because of a functional neuro-endocrine failure in homeostasis.—[Author's summary.]

396. Anticipated Clinical Course in Carotid Artery Occlusion

W. G. HARDY, D. W. LINDNER, L. M. THOMAS, and E. S. GURDJIAN. *Archives of Neurology* [Arch. Neurol. (Chic.)] 6, 138-150, Feb., 1962. 11 refs.

Data concerning the natural history of carotid artery thrombosis are meager, and the problems facing those trying to assess therapy in vascular disease are immense. The mode of onset of symptoms in 153 patients with carotid occlusion was studied. Changes in the clinical conditions of these patients according to the grades of severity were recorded at the time of onset of symptoms, when diagnosis was established, and at follow-up. Function status at the end of 3-7 year (average) follow-up was ascertained.

Ninety-eight of the patients were treated surgically, primarily by excision of the occluded vessel. Anticoagulants were seldom used in treatment. Very little difference was noticed in the outcome of the surgically and conservatively treated patients, and the clinical course of the entire group is presented in an indication of the probable course of the disease. The patients whose onset of symptoms was sudden had more severe neurological deficits when seen than patients with episodic symptoms. They were also more acutely ill, and 31% of those dying died within one month of onset. Those that were able to survive the initial onslaught of the stroke continued to live for long periods of time, with improvement of function in many. This probably is due to collateral circulation existent before the sudden thrombotic attack. Those with episodic cerebral ischaemic attacks may have this type of onset because of gradual decompensation of collateral cerebral circulation. As the disease progresses they continue to have more and more attacks and a greater number of repeated strokes. Even though there may be progression of the pathological processes in the group with sudden onset, if they have enough collateral circulation to survive initially there are fewer recurrences of completed stroke than in the episodic group.

Those with progressive onset of symptoms did poorest, with completion of stroke an average of 4-5 months after onset of symptoms and progression to death within one year in 62%. Seventy-one of the 153 patients have died; 28% died from original stroke, 27% died from repeat stroke, 15% died from other causes, and the cause was not accurately known in 30%. 66% died more than one year from the onset of symptoms. Age at onset of symptoms is a factor determining survival of the initial completed stroke, as is the presence of associated disease. . . . The majority of those

who died of a recurrent stroke had severe initial deficits and regained very little function before the second attack, whereas those who survived a repeat attack had regained function, or were not as severely crippled by their original stroke. Slightly over 50% of the patients having repeated transient ischaemic attacks after a completed stroke had another stroke, and about 75% died from subsequent stroke.—[From the authors' summary.]

397. Adaptation of the Circle of Willis to Occlusion of the Carotid or Vertebral Artery: Its Implication in Carotico-vertebral Stenosis

R. D. LOWE. *Lancet* [Lancet] 1, 395-398, Feb. 24, 1962. 5 figs., 18 refs.

At University College Hospital, London, ophthalmodynamometric studies were made on 10 patients who had long-standing occlusion of one common carotid artery. The retinal pressure on the side of the occlusion was lower than on the healthy side, but the difference between the two sides was less than the difference observed between the two sides in healthy people when one common carotid artery was compressed. In the patients with carotid occlusion compression of the healthy vessel caused the retinal pressure in both eyes to fall, the fall being greater on the side of the healthy vessel than on the side of the occlusion. These findings are interpreted as indicating that after long-standing occlusion of the common carotid artery collateral channels develop which cause the pressure to return towards normal. Much of the collateral supply comes from the opposite carotid artery via the anterior communicating artery, but there is also a substantial contribution from the vertebral artery via the posterior communicating artery. Results leading to similar conclusions were obtained after ligation of the common carotid artery in rabbits. This procedure was followed by enlargement of the posterior communicating artery, which was demonstrated by resin casts of the vessels. The author considers that his findings throw doubt on the view that stenosis of the carotid and vertebral arteries is a significant factor in over-all cerebrovascular resistance. The relevant literature is briefly and critically reviewed. *Bernard Isaacs*

398. Acute Necrotizing Encephalitis: a Diagnostic Problem in Temporal Lobe Disease. Report of Three Cases

D. R. BENNETT, G. M. ZURHEIN, and T. S. ROBERTS. *Archives of Neurology* [Arch. Neurol. (Chic.)] 6, 96-113, Feb., 1962. 9 figs., 39 refs.

The term acute necrotizing encephalitis was coined by van Bogaert *et al.* (*Rev. Neurol.*, 1955, 92, 329) to designate a form of meningoencephalitis characterized by softening of the temporal lobes and related rhinencephalic structures with extensive necrosis, of which they described one case. During the past 20 years 59 cases with similar clinical and anatomical findings have been reported in the literature, omitting those in patients under one year of age. The disease is most prevalent during the first five decades of life, especially the third. Approximately one-third of the patients had a history of predisposing ailment at the onset or just before, colds, sore throat, and gastro-intestinal disturbances being the most common. In several cases head injury, electric convulsion therapy, or intense physical exercise had immediately preceded the illness. The onset is abrupt, with headache, high fever, nausea and vomiting, meningeal signs, and generalized convulsions, these being soon followed

by signs suggestive of temporal lobe involvement, while increased intracranial pressure is commonly found.

In this paper from the University of Wisconsin Hospitals, Madison, the detailed histories and pathological changes in 3 further cases are described. Type-A intranuclear inclusions were present in all cases. Culture of brain tissue for the presence of virus, performed in one case, was negative. The occurrence of the disease as an acute intracerebral mass, especially of the temporal lobe, was corroborated by similar cases among the 59 reported in the literature. The histological differences between acute necrotizing encephalitis and the well-established viral encephalitis are enumerated, while the vascular alterations in one case, which were suggestive of a hypersensitivity reaction, are described. Clinical and laboratory aids to diagnosis, though helpful, are not specifically diagnostic. Only by the finding of Type-A intranuclear inclusions in association with the other histological changes found in brain biopsy specimens can an ante-mortem diagnosis be made. *J. MacD. Holmes*

399. **The Use of Micropaque Barium Sulphate in the Treatment of Abscesses of the Brain.** [In English]

P. R. R. CLARKE, C. LANGMAID, and S. WRAY. *Neurochirurgia [Neurochirurgia (Stuttg.)]* 4, 211-217, Feb., 1962. 7 figs., 4 refs.

The injection of contrast material into an intracranial abscess to permit visual estimation of its size has been routine neurosurgical procedure for many years. "Thorotrast", which is 24% colloidal thorium dioxide, has been the substance generally used until recently. The advantages of thorotrast are its persistence and rapid concentration in the abscess wall; the disadvantages are its capacity for stimulating late neoplastic change in the body and the possibility that the excess fibrosis which occurs in the wall of the abscess after injection may be a factor in the aetiology of epilepsy.

In this paper from the Cardiff Royal Infirmary and the General Hospital, Middlesbrough, a trial is reported of "steripaque", which is 100% weight/volume suspension of particles of micro-opaque barium sulphate varying in size between 0.1 and 0.5 μ . It was used in 8 cases of brain abscess with completely satisfactory results. The authors state that when steripaque is mixed with appropriate antibiotics it forms a thick cream which remains within the abscess cavity instead of leaking along the track of the withdrawn cannula. In about a week concentration of the barium in the wall of the abscess can be seen radiologically, and from that time enlargement or contraction of the cavity can be followed. Re-aspiration of the abscess does not appear to affect the density of the shadow. The greatest advantage of barium sulphate over thorotrast is its completely inert nature, making persistence of this contrast material in brain or ventricle a matter of no great concern. *J. V. Crawford*

400. **Tentorial Meningiomas**

H. S. BARROWS and D. H. HARTER. *Journal of Neurology, Neurosurgery and Psychiatry [J. Neurol. Neurosurg. Psychiat.]* 25, 40-44, Feb., 1962. 8 refs.

A series of 24 cases of verified primary tentorial meningiomas, seen at the New York Neurological Institute between 1932 and 1950, is analysed. In 8 cases the tumours were seen to extend both supra- and infra-tentorially. Clinically, a distinction was noted between tumours principally supra-

tentorial and those principally infratentorial. In 8 patients extension occurred supra-tentorially into the occipital or temporal lobes.

The clinical picture in this series was that of a unilateral cerebral lesion, the tentorial origin being rarely appreciated when the patient was admitted. The cerebrospinal fluid (C.S.F.) was under normal pressure, with a raised protein content. The electroencephalogram accurately indicated the involved hemisphere. In 16 patients extension occurred infratentorially and provided clinical enigmas. In 6 of these the picture was that of obstructive hydrocephalus; the prognosis was poor. In 6 others in this group symptoms were referable to the trigeminal nerve, often with eighth-nerve involvement. The prognosis in this group was relatively good. The remaining 4 patients had complex disturbance of gait; the prognosis was relatively good. In all the cases of infratentorial tumour there were signs of cerebellar involvement. Skull radiographs and examination of the C.S.F. were not helpful in diagnosis. *R. Wyburn-Mason*

401. **The Migrainous Symptoms of Cerebral Angiomata**

F. LEES. *Journal of Neurology, Neurosurgery and Psychiatry [J. Neurol. Neurosurg. Psychiat.]* 25, 45-50, Feb., 1962. 16 refs.

The author of this paper from the Royal Infirmary, Manchester, and St. Bartholomew's Hospital, London, describes a study of 70 patients with proven cerebral angiomata, with special emphasis on migraine-like symptoms. It is pointed out that although the symptoms may simulate migraine, especially when the angioma is in or near the occipital lobe, it is rare to encounter the complete migraine syndrome, as evidenced by alternating hemiparesis, accompanied or preceded by visual symptoms such as teichopsia, flashes of light, or hemianopia and often by paraesthesiae, paresis, and dysphasia, followed by nausea and vomiting. Examination of a patient with headache is unlikely to reveal an angioma of the brain unless the headache and aura are persistently one-sided or unless it reveals abnormal neurological signs or cranial bruit. *R. Wyburn-Mason*

402. **Clinical Picture of Brain Tumours in Children in the First Three Years of Life.** (Клиника опухолей головного мозга у детей первых трех лет жизни)

E. S. BONDARENKO. *Вопросы Охраны Материнства и Детства [Vop. Okhrany Materin. Dets.]* 7, 17-23, Feb., 1962. 12 refs.

An analysis of 21 cases of brain tumour in children under 3 years of age bears out the opinion of many authors as to the predominance in this age-group of dysontogenetic neoplasms situated in the midline, and also as to the difficulty of making an early diagnosis. The various sites of the tumours were as follows: cerebellum in 8 cases, fourth ventricle in 3, third ventricle in 1, lateral ventricle in 2, cerebral hemispheres in 5, and the meninges in 2; while as to type, 4 were medulloblastomata, 4 ependymomata, 2 multiform glioblastomata, 2 papillomata of the vascular network, 2 astrocytomata, one sarcoma, and one neuroma. In 5 cases no histological evidence was available.

The presenting symptoms, in order of frequency, were: change in behaviour, usually in the direction of somnolence, more rarely irritability; headaches of paroxysmal type and of increasing severity; vomiting; and epileptiform convul-

sions, more often of tonic type and sometimes followed by hemiparesis. The symptoms often simulated those of meningitis. The most constant physical signs were papilloedema (noted in 10 of the 21 cases) and an increase in head circumference. The spinal fluid showed an increase in protein content and lymphocytic pleocytosis, but xanthochromia was less common; in some cases the glucose content was low. In 4 cases the spinal fluid was normal. Of the 8 children subjected to operation [details not given] 6 were discharged relieved and 2 died.

L. Firman-Edwards

EPILEPSY

403. Electrocorticography during Operation for Partial Epilepsy

O. MAGNUS, A. C. DE VET, A. VAN DER MAREL, and E. MEYER. *Developmental Medicine and Child Neurology* [*Develop. Med. Child Neurol.*] 4, 35-48, Feb., 1962. 3 figs., 18 refs.

Some of the problems of surgical treatment of partial epilepsy are discussed in this paper, the authors drawing on their own experience of 45 cases so treated between 1949 and 1953 at the St. Ursula Neurological Clinic, Wassenaar, Netherlands. Difficulties in the selection of cases for surgical treatment are illustrated and the limitations of diagnostic methods, including electroencephalography, electrocorticography, and direct cortical stimulation, in delimiting the area for excision are discussed. Follow-up studies of the authors' 45 patients showed that 19 were free from seizures, 15 had only occasional seizures, and 9 have not been improved; 2 patients died from the operation.

The authors conclude that the concept of a small restricted epileptic focus in cases of partial epilepsy does not in many cases accord with the facts. Even in cases of so-called focal epilepsy the pathological and electrical abnormalities are often found to be more widespread and complex. Nevertheless, it is suggested that a considerable number of patients with partial epilepsy resistant to drug therapy will benefit from surgery, particularly as locating methods become more exact.

J. B. Stanton

404. Comparison of the Effectiveness of Phenobarbital, Mephobarbital, Primidone, Diphenylhydantoin, Ethotoin, Metharbital, and Methylphenylethylhydantoin in Motor Seizures

C. M. GRUBER JR., J. T. BROCK, and M. DYKEN. *Clinical Pharmacology and Therapeutics* [*Clin. Pharmacol. Ther.*] 3, 23-28, Jan.-Feb., 1962. 2 figs., 7 refs.

The authors' summary reads as follows. "Forty-four patients with focal brain damage and epilepsy were given phenobarbital, mephobarbital, primidone, diphenylhydantoin, ethotoin, metharbital, methylphenylethylhydantoin, and blank on a double blind basis as replacement of their usual anticonvulsant medications. The number of seizures observed provided a score which was used to determine drug effectiveness.

"The results indicate that the patients differed with regard to the severity of the epilepsy, their response to medication and dose, and their response during 5 days of study. With effective doses of medication, the seizure scores increased more slowly than when ineffective doses were given. With all of the treatments except the blank and the smaller doses

of diphenylhydantoin and ethotoin, there was an inverse relationship between the dose and the seizure scores."

The doses of the drugs which were calculated to be equally effective were: phenobarbital 30 mg., diphenylhydantoin 200 mg., methylphenobarbital 128 mg., primidone 93 mg., methylphenylethylhydantoin 112 mg., and metharbital 110 mg. Doses of 70 mg. of diphenylhydantoin and 470 mg. of ethotoin appeared to lower the seizure scores equally. The authors conclude that "five days of observation of patients with focal brain damage and epilepsy is sufficient to evaluate the effectiveness of drugs in suppressing motor seizures". They state that the results may not reflect the effectiveness of the drugs in epilepsy or in all situations.

J. MacD. Holmes

405. EEG Response to Photic Stimulation in 120 Normal Children. [In English]

H. BRANDT, S. BRANDT, and K. VOLLMOND. *Epilepsia* [*Epilepsia (Amst.)*] 2, 313-317, Dec., 1961 [received Feb., 1962]. 3 figs., 8 refs.

This paper from Dronning Louises Børnehospital, Copenhagen, warns against too facile diagnosis of epilepsy in children solely on the basis of paroxysmal responses in the electroencephalogram on photic stimulation. The authors found that 31 (25.8%) of 120 normal children showed either generalized paroxysmal bursts or solitary slow waves of high amplitude in both occipital areas. No such responses were found in the 25 children in the group who were over 15 years of age, and if these are excluded the percentage of positive responses rises to 32.6%.

The authors hold the view that paroxysmal responses to photic stimulation are largely dependent on constitutional factors whose influence decreases as cerebral maturation proceeds.

J. B. Stanton

406. Urinary Excretion of Electrolytes in Centrencephalic Epileptics. [In English]

J. SCHNEIDER. *Epilepsia* [*Epilepsia (Amst.)*] 2, 358-366, Dec., 1961 [received Feb., 1962]. 3 figs., 35 refs.

Studying 43 patients with frequent and intractable petit-mal epilepsy (some with rare grand-mal seizures) at the Hôpital Pasteur, Colmar, Haut-Rhin, France, the author found correlations between changes in the electroencephalogram and clinical state and the urinary electrolyte excretion. Generally speaking, sodium and water retention preceded exacerbations of the epilepsy, and increased excretion of sodium and water accompanied clinical and electrical improvement. Calcium output appeared to parallel that of sodium, while the potassium excretion varied inversely with that of sodium. The retention of water and sodium occurs at the intracellular level, leading to relative depolarization of the neurones, which in turn gives rise to epileptic discharges.

The author discusses the theoretical possibilities that centrencephalic epilepsy may be due either to a systemic metabolic or electrolyte disorder only secondarily involving the brain, or to a primary cerebral dysfunction involving the diencephalic structures, which are then responsible for the generalized electrolyte disturbances. Anticonvulsants and sometimes ACTH (corticotrophin) may exert their beneficial effect by favouring a more satisfactory distribution of electrolytes across the cellular membrane and by correcting the systemic electrolyte disturbance.

J. B. Stanton

Psychiatry

407. Evaluation of Calcium Carbimide in the Treatment of Alcoholism

M. BRUNNER-ORNE. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 163-167, Feb., 1962. 15 refs.

Until recently disulfiram ("antabuse") was the main drug used therapeutically to produce systematic reaction after the ingestion of alcohol, the unpleasant symptoms caused helping to prevent the patient drinking. Another substance, citrate calcium carbimide (C.C.C.; "temposil") has recently been found to produce reactions to alcohol similar to (though less severe than) those produced by disulfiram.

This paper from the New England Hospital, Boston, reports a comparison of the effects of C.C.C., which was given in 53 cases of alcoholism, with those of disulfiram. It was confirmed that the reaction to alcohol with C.C.C. (which was tested in a few cases only) was similar to that with disulfiram, but the side-effects—such as lethargy, halitosis, and impotence—which are fairly common in patients taking disulfiram, did not occur with C.C.C. More important, the severe cardiovascular effects that may occur when a disulfiram-alcohol reaction takes place are not seen with C.C.C. On the other hand disulfiram is excreted slowly and its effects persist for several days; whereas C.C.C. is rapidly excreted and its effects do not persist for more than 24 hours so that it is necessary to take the drug regularly at comparatively short intervals (preferably 12-hourly). It is emphasized that the use of either of these drugs can be only a part of the total treatment of an alcoholic.

B. M. Davies

408. The Comparative Effectiveness of Six Phenothiazine Compounds, Phenobarbital and Inert Placebo in the Treatment of Acutely Ill Patients: Personality Dimensions

A. A. KURLAND, M. H. MICHAUX, T. E. HANLON, K. Y. OTA, and A. M. SIMOPOULOS. *Journal of Nervous and Mental Diseases* [*J. nerv. ment. Dis.*] 134, 48-61, Jan. [received April], 1962, 1 fig., 17 refs.

In comparing the effect on 238 actively disturbed patients at Spring Grove State Hospital, Baltimore, of 6 phenothiazine drugs, phenobarbitone, and a placebo, primary and second order M.S.R.P.P. (Multidimensional Scale for Rating Psychiatric Patients) factors, ward behaviour, and clinical psychiatric condition were assessed separately. When variations in the drug scores were found, inter-relational change of score suggested that the factors affected by the drugs could be grouped into three broad areas—conceptual disorganization, perceptual disorganization, and thinking disorder forming one group, paranoid belligerence and the bipolar factor self-depreciation/grandiosity the second, and withdrawal forming the third.

A comparison of drugs in the first or ideational group showed chlorpromazine to be outstandingly effective, the mean score of patients receiving it being lower after treatment than with any other drug. A striking pattern was found in the second group. Mepazine (pecazine) and promazine (the least effective in the over-all study) lowered self-

esteem, phenobarbitone and the placebo raised it, and the other drugs tended to bring the score to the middle of the bipolar scale. The drugs tending to lower self-depreciation also increased withdrawal. The most effective in improving this symptom was perphenazine. Chlorpromazine tended to make the patient drowsy, giving a negative withdrawal effect.

Differential regressions and variances were studied. Generally speaking, the more effective the drug, the slighter the relationship between pre-treatment state and the result, and the more similar, in respect of individual symptoms, the patients are to one another after treatment.

E. H. Johnson

409. Intravenous Atropine Premedication before Electroconvulsion Therapy

M. A. HARGREAVES. *Lancet* [*Lancet*] 1, 243, Feb. 3, 1962. 7 refs.

The author of this paper from the United Birmingham Hospitals attempts to show that intravenous injection of atropine immediately before electric convulsion therapy (E.C.T.) is adequate and has advantages over the more usual subcutaneous route. The effect of atropine by both the intravenous and subcutaneous routes was studied in 200 patients undergoing E.C.T., each of whom received at least 6 treatments. Usually the atropine was given in the same syringe as thiopentone. It was found that salivation occurred equally after subcutaneous and after intravenous injection of atropine in 190 of the patients; in the remaining 10 no suppression of saliva occurred, irrespective of the route or of the dosage. The advantages of intravenous injection include ease of administration, especially in outpatients, and absence of a period of discomfort before treatment. There appeared to be no disadvantages of this method of administration.

J. S. Bearcroft

410. Changes in the Photically-driven EEG following Electroconvulsive Therapy

G. ULETT, K. DAS, F. HORNING, D. DAVIS, and M. JOHNSON. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 186-189, Feb., 1962. 4 figs., 8 refs.

Observations have shown that after electric convulsion therapy (E.C.T.) there are consistent changes in the electroencephalogram (EEG). These include diffuse slowing with increased voltage and dysrhythmic activity.

In this study, reported from the Malcolm Bliss Mental Health Center and Washington University School of Medicine, St. Louis, EEGs were recorded from 20 patients during intermittent photic stimulation both before and after a course of E.C.T. The results were analysed and showed that E.C.T. produces an over-all depression of those brain structures which normally respond to the intermittent flashing light stimulus. This depression, however, is reversible, and 2 weeks after treatment the response has returned to pre-shock level. It is not known whether these effects depend on cortical or brain-stem functions.

B. M. Davies

Dermatology

411. The Biology of Experimental Human Cutaneous Moniliasis (*Candida albicans*)

H. I. MAIBACH and A. M. KLIGMAN. *Archives of Dermatology* [Arch. Derm.] 85, 233-257, Feb., 1962. 12 figs., 31 refs.

The authors, working at the University of Pennsylvania, Philadelphia, have observed approximately 1,000 cutaneous infections induced experimentally with *Candida albicans* in 150 healthy subjects. In order to produce any skin changes at all it was found necessary to occlude the area of application of the *Candida* inoculum with a waterproof tape; lesions then developed in 36 to 72 hours as small, discrete, tense pustules on an erythematous background. Histologically these were subcorneal pustules and it was noted that the organism had no penetrating powers but was restricted to the outer limits of the stratum corneum.

The season of the year did not affect the characteristics of the experimental infection nor did reduction in the local bacterial flora by means of topical or systemic antibiotics. Similarly the infection was not potentiated by the use of systemic or local steroids. The forearms, thighs, and trunk could be infected with ease, but the palms of the hands were resistant. Lesions resembling erosio interdigitalis could be produced if rubber gloves were worn. Secondary monilial infections, however, could not be induced when organisms were applied to areas of psoriasis or lichen simplex or to areas subject to experimental trauma by freezing or ultraviolet light irradiation. Concomitant use of a 1% aqueous solution of gentian violet or nystatin cream prevented the development of the infection.

As regards allergy and immunology, no evidence was found of an acquired hypersensitivity in subjects who were infected for 5 consecutive weeks and agglutinins did not increase after repeated cutaneous infections.

A sterile extract of disintegrated *Candida* cells and a sediment of killed, ruptured cells reproduced the typical features of cutaneous moniliasis when applied as a patch test. The authors suggest, therefore, that the pathological reaction in cutaneous moniliasis is mediated by endotoxin-like substances released by the organism on the surface and hence that cutaneous moniliasis is a biological contact dermatitis of the primary irritant type.

Benjamin Schwartz

412. A Controlled Trial of Oral Antibiotics in the Treatment of Acne Vulgaris

M. A. SMITH, P. M. WATERWORTH, and M. P. CURWEN. *British Journal of Dermatology* [Brit. J. Derm.] 74, 86-90, March, 1962. 7 refs.

In a carefully conducted double-blind trial at St. Bartholomew's Hospital, London, 60 patients with acne received for a period of 4 weeks phenethicillin ("broxil", 250 mg. 4 times daily), demethylchlortetracycline ("ledermycin", 150 mg. 4 times daily), or placebo tablets, the cases being divided by random allocation into 3 approximately equal groups. Results were assessed by diary cards kept by the patients, photographs of patients taken before and

after treatment, and clinical assessment by the same physician.

No clear difference emerged between the 3 groups by whichever method the assessment was made, but there appeared to be genuine improvement in the majority of the patients, which was less in the placebo group than in either antibiotic group. Thus, though the differences were not statistically significant, it was thought possible that either antibiotic did have a real effect on a proportion of patients and that a larger trial should be conducted to test this. Acne bacilli were cultured from most of the lesions, but *Staphylococcus pyogenes* was not isolated from any specimen.

E. W. Prosser Thomas

413. The Treatment of Acne Vulgaris with Epioestriol ("Actriol")

R. J. RUSHTON. *British Journal of Dermatology* [Brit. J. Derm.] 74, 91-93, March, 1962. 11 refs.

The results of a double blind trial of local epioestriol ("actriol") in the treatment of acne vulgaris are reported. The steroid failed to produce any significant effect.—[Author's summary.]

414. The Treatment of Psoriasis with Vitamin A and Triamcinolone. Interim Report

C. H. WHITTLE, B. WOODS, R. V. GRANGE, R. G. CARPENTER, and J. A. CASBOLD. *British Journal of Dermatology* [Brit. J. Derm.] 73, 433-438, Dec., 1961. 1 fig., 27 refs.

An ointment containing vitamin A and triamcinolone acetate has been tried in 41 cases of bilateral psoriasis at the United Cambridge Hospitals. Patients were given 2 containers marked respectively L and R, one containing the ointment under trial and the other a similar cream with triamcinolone alone, and instructed to apply each preparation twice daily on the appropriate side. In 5 cases there were no detectable changes on either side, 5 cases showed equal improvement on both sides, and in 31 cases there was greater improvement on one side than the other. Of these, 23 showed a more favourable response to the vitamin-A ointment and 8 a more favourable response to the control ointment.

G. B. Mitchell-Heggs

415. The Treatment Time in Psoriasis

M. MACLENNAN and F. F. HELLIER. *British Journal of Dermatology* [Brit. J. Derm.] 73, 439-444, Dec., 1961. 1 fig., 9 refs.

The authors analyse the results of treatment in 2,120 cases of psoriasis seen at the General Infirmary at Leeds during the years 1958-60. In all cases the Ingram method of treatment (*Brit. med. J.*, 1953, 2, 591; 1954, 2, 823; *Abstr. Wld Med.*, 1954, 15, 261), the most important feature of which is the application of dithranol in Lassar's paste, was used. Successful results were obtained in 2,034 cases (95%). The median times for clearing of the skin lesions were 15.2 days for in-patients and 19.5 days for out-patients. It was found that injections of cyanocobalamin did not influence the speed of response in these cases.

G. B. Mitchell-Heggs

Paediatrics

416. **Eosinophilic Disease in Children.** (Об эозинофильной болезни у детей)

V. V. ŠICKOVA-MARTYNKINA. *Педиатрия [Pediatrya]* 40, 79-83, Feb., 1962. 9 refs.

The author describes the cases of 4 children who came under her observation with the presenting syndrome of catarrh, lymphadenopathy, splenomegaly, hepatomegaly, and anaemia. Blood counts revealed a high degree of eosinophilia (11 to 24%) and marrow puncture examination showed an excess of mature eosinophil granulocytes. In one case only was *Ascaris* infection present, this being definitely excluded in the other 3. The patients were 2 boys aged 3 and 10 years respectively and 2 girls aged 4 and 10. The disease progressed in an undulating course over a period varying from 9 months to 2½ years; the onset was acute in 3 cases and gradual in the 10-year-old girl.

Treatment consisted in administration of a full, balanced, diet with abundant vitamins, calcium preparations, blood transfusions as indicated, prednisone, and in 2 cases penicillin. No causative factor was found, but the history and clinical findings suggested an infective origin. All 4 children became clinically well, but the eosinophilia has to some degree persisted. A similar condition was first described by Walleder in the U.S.A. in 1945, and later by numerous other workers in various countries. Goldstein called the condition infectious eosinophilia, Bousser regarded it as a "disseminated eosinophil collagenosis", while Polenko termed it "progressive reactive-allergic reticulo-endotheliosis".

L. Firman-Edwards

417. **Ulcerative Colitis in Childhood: a Study of 43 Cases**

J. C. HUMANS and N. B. ENZER. *Pediatrics [Pediatrics]* 29, 389-403, March, 1962. 5 figs., 47 refs.

Between 1932 and 1960, 43 children (24 male and 19 female) with ulcerative colitis were seen at the Duke University Medical Center, Durham, N. Carolina. The condition is relatively rare in negro children, there being only 5 negroes in the series. The onset was insidious in 24 and fulminating in 19. The disease occurred at all ages in childhood (in the first month of life in 3 instances), but there was a marked increase in incidence in the pre-adolescent and adolescent periods.

Clinically there were the usual classic features, namely, bloody diarrhoea, abdominal pain and tenesmus, loss of weight, and an abnormal mucosa. The most frequent abnormal findings were changes in the colon on barium-enema examination, anaemia, a high erythrocyte sedimentation rate, and an inverse albumin:globulin ratio. The condition was classified as "severe" in 28 patients or "mild to moderate" in 15.

The course of the disease was not influenced by age at onset, the type of onset, or the duration of the illness. Local complications were noted in 18 cases but no malignant changes were observed. There were various extra-colonic changes such as anaemia, rashes, stomatitis, arthropathy, clubbing, hepatosplenomegaly, and pancreatitis. Assessment of the patients at the time the paper was written

showed that there was prolonged remission in 12, much improvement in 5, and persistence of symptoms in 19; the remaining 7 patients had died. Treatment was with "sulpha" drugs and corticosteroids, operation being performed in 5 cases.

It is concluded that ulcerative colitis in childhood is serious, the diagnosis difficult, the course variable, and the prognosis unpredictable.

John Fry

418. **Congestive Heart Failure in Infancy: Significance of the Venous Pressure**

A. J. MOSS and E. R. DUFFIE JR. *Journal of Pediatrics [J. Pediat.]* 60, 346-351, March, 1962. 1 fig., 14 refs.

It is pointed out in this paper from the University of California, Los Angeles, that cardiac failure in infancy manifests itself by tachypnoea, tachycardia, and hepatomegaly, and only rarely by peripheral oedema or venous distension. The authors therefore recorded at cardiac catheterization the right atrial pressure in 22 children under the age of 2 years whose case records indicated the presence of cardiac failure and also in 17 children suffering from similar congenital cardiac defects whose records contained no such evidence.

The average mean right atrial pressure in the group with cardiac failure was 5.6 mm. Hg, compared with 5.4 mm. Hg in the controls. Of the 22 children with failure, 5 died within 24 hours of the catheterization; the average mean right atrial pressure in these 5 was 7.7 mm. Hg. The unexpectedly low atrial pressure in failure was not thought to be due to a decrease in the intrathoracic pressure accompanying laboured breathing, because similar low values were recorded in the extrathoracic portion of the inferior vena cava.

The authors conclude that different mechanisms may account for cardiac failure in this age group which should be further investigated. They emphasize [it is important to note] that these children received basal anaesthesia with thiamylal administered per rectum and also digitalis, which may have affected the findings.

H. G. Farquhar

419. **Specific Malabsorption of Vitamin B₁₂ with Proteinuria (Megaloblastic Anaemia of Imerslund, Najman, and Grasbeck). (A Study of Four Cases).** (La malabsorption spécifique de la vitamine B₁₂ avec protéinurie (l'anémie mégaloblastique d'Imerslund-Najman-Grasbeck). (Etude de quatre cas))

M. LAMY, F. BESANÇON, A. LOVERDO, and F. AÏFI. *Archives françaises de pédiatrie [Arch. franç. Pédiat.]* 18, 1109-1120, Oct., 1961 [received March, 1962]. 12 refs.

The authors report from the Hôpital des Enfants-Malades, Paris, 4 cases of megaloblastic anaemia associated with proteinuria due to a specific malabsorption of vitamin B₁₂ occurring in young children, to which they add 5 cases collected from the literature. The anaemia may appear in the first year of life and is often severe; thrombocytopenia may also be found. Achlorhydria is not always present and free acid, if absent in the anaemic phase, returns during remissions. The presence of intrinsic factor was demon-

strated in at least one patient. Failure to absorb small doses of vitamin B₁₂ was confirmed by tests with labelled vitamin, though the authors comment on the fact that very large doses (12,000 mg. administered over 2 weeks) gave a reticulocyte response. In treatment vitamin B₁₂ or liver extract by parenteral injection is effective.

Among the 9 cases described glossitis and neurological signs were variable in their occurrence. Some of the patients presented with psychological disturbances. In some cases the syndrome appeared to be familial. The authors consider that steatorrhoea and infestation with *Bothriocephalus latus* can both be ruled out as aetiological factors and suggest that the fundamental lesion is a congenital failure to absorb vitamin B₁₂ in the ileum. There is some evidence that spontaneous cure may take place between the ages of 20 and 30 years.

Janet Vaughan

420. A New Classification of Megaloblastic Anaemia of Infancy Due to Primary Avitaminosis B₁₂. (Nouvelle classification des anémies mégaloblastiques infantiles par avitaminose B₁₂ primitive) M. LAMY and F. BESANÇON. *Archives françaises de pédiatrie* [*Arch. franç. Pédiat.*] 18, 1121-1127, Oct., 1961 [received March, 1962]. 10 refs.

The authors propose a new classification of the megaloblastic anaemias of infancy due to lack of vitamin B₁₂, as follows. (1) Pernicious anaemia with all the classic signs and symptoms, particularly permanent achylia. (2) Lack of intrinsic factor without lack of free acid. (3) Malabsorption of vitamin B₁₂, accompanied by proteinuria but no lack of intrinsic factor or free acid. (4) Absence of intrinsic factor associated with a specific malabsorption of vitamin B₁₂. Theoretically the authors consider it possible to treat all megaloblastic anaemias with massive oral doses of vitamin B₁₂, but in practice they have found parenteral injection to be cheaper and more satisfactory. They suggest that when patients reach the age of 30 they should be specifically investigated to determine if there has been spontaneous remission. They urge that radioactive isotopes should not be used in the investigation of young children.

Janet Vaughan

421. Etiology and Course of Certain Hemiplegias with Aphasia in Childhood

R. K. BYERS and W. T. MCLEAN. *Pediatrics* [*Pediatrics*] 29, 376-383, March, 1962. 5 figs., 6 refs.

The authors report on 12 cases of hemiplegia with aphasia, of which 11 were seen at the Children's Hospital, Boston, between 1947 and 1955 and one at the Memorial Hospital, Charlotte, North Carolina, in 1958. The patients' ages ranged from 3 to 15 years, but 7 were between 5 and 10 years old. In 7 cases the full syndrome developed within 24 hours of onset, while in 5 the history was prolonged and not typical until the characteristic features emerged. In one patient there was a history of possible embolism and 2 had suffered mild trauma, but no other precipitating factors were found. Arteriograms were obtained in 7 cases and in 6 of these showed vascular malformations or thrombosis. An arterio-venous aneurysm was extirpated in a 13-year-old boy, but his hemiplegia and partial aphasia persisted. This patient had a history of previous attacks, one 6 years previously, from which he fully recovered, and another 1 year previously when recovery was only partial. A

thrombosis was removed from the left internal carotid artery in another patient, but no immediate improvement in signs occurred.

Of 10 patients followed up 3 to 7 years later, all had regained speech, 4 appear intact, the others have residual lesions, and 2 have had recurrent seizures.

Janet Q. Ballantine

422. Neurological and Ophthalmic Disorders in Children of Very Low Birth Weight: a Survey with the Society of Medical Officers of Health

A. D. McDONALD. *British Medical Journal* [*Brit. med. J.*] 1, 895-900, March 31, 1962. 6 refs.

Of the children included in an investigation into the association between oxygen therapy and retrolental fibroplasia which was carried out under the auspices of the Medical Research Council on all infants weighing under 4 lb. (1,800 g.) at birth who were born between October 1, 1951, and May 31, 1953, 1,128 survived for 6 months. These same children have now been followed up, as from March, 1959, and the author here presents a preliminary report on the results.

Of the 1,128 children, 19 were untraced and 28 had died. Of these latter, 15 (54%) had neurological disorders, 3 had retrolental fibroplasia, and one, whose mother had had rubella during the pregnancy, had cataracts. Of the 1,081 remaining children, 244 (22.6%) had neurological or severe ophthalmic disorders, while 71 children (6.6%) had cerebral palsy and in at least 68% and probably 80% of these it was of the spastic diplegic type. Mental retardation to an ineducable degree was found in 29 cases (2.7%), 102 (9.4%) had a history of one or more fits, 24 (2.2%) had other neurological disorders, 20 (1.9%) were blind as a result of retrolental fibroplasia, 35 (3.2%) had severe visual defects, and 19 (1.8%) were moderately or severely deaf. No association was found between cerebral palsy and retrolental fibroplasia.

Janet Q. Ballantine

423. Congenital Ataxic Syndromes in Cerebral Palsy. [In English]

T. T. S. INGRAM. *Acta paediatrica* [*Acta paediat. (Uppsala)*] 51, 209-221, March, 1962. 29 refs.

Ataxic syndromes have attracted less attention in the past than other forms of cerebral palsy, yet recent surveys suggest that more than 10% of patients with cerebral palsy are ataxic. Analysis of case reports in the literature leads to the differentiation of two forms of ataxic cerebral palsy. "Ataxic" patients have very retarded motor milestones and are hypotonic. They show unsteadiness, inco-ordination of voluntary movement and intention tremor. They walk flat-footed with their legs wide apart. Patients with "ataxic diplegia" are hypotonic in early infancy but later show spastic paresis more severe in the lower limbs than the upper, in addition to the signs of ataxia. (They walk on their toes with greater or lesser degrees of adductor spasm.) A proportion are epileptic.

The clinical findings in a series of 60 patients with congenital ataxia seen in two Edinburgh clinics are reviewed. It is suggested that developmental malformations may be of greater aetiological importance than birth injury in both "ataxia" and "ataxic diplegia". The course and clinical findings of both types of ataxic cerebral palsy are described and compared.—[Author's summary.]

Public Health and Industrial Medicine

424. Antigenic Response to Booster Dose of Diphtheria and Tetanus Toxoids Seven to Thirteen Years after Primary Inoculation of Noninstitutionalized Children

V. K. VOLK, R. Y. GOTTSHALL, H. D. ANDERSON, F. H. TOP, W. E. BUNNEY, and R. E. SERFLING. *Public Health Reports [Publ. Hlth Rep. (Wash.)]* 77, 185-194, March, 1962. 5 refs.

A booster dose of 2 Lf units each of diphtheria and tetanus toxoids resulted in prompt and vigorous increases in the circulating antitoxin levels in a group of 174 children who had received 3 primary immunizing injections 7 to 13 years previously, and this occurred also even in the few subjects whose primary immunization was limited to one or two injections. This response to the booster injection was maximal at 2 weeks, but was still measurable 2 years later. No undesirable reactions were produced by the booster dose.

This study is held to justify reconsideration of the intervals at which booster doses have been recommended (3 to 4 years) for continued protection against diphtheria and tetanus. Routine booster doses need not be given until 5 years have elapsed since primary immunization, but a booster is indicated in special circumstances of exposure to either of these diseases, or if they become prevalent in any locality, or during abnormal crowding or displacement of a population at a time of disaster.

H. Stanley Banks

425. A Study of Cancer Mortality in Farming, Quarrying, Mining and Other Occupations in North Wales and Cheshire P. STOCKS. *British Journal of Cancer [Brit. J. Cancer]* 15, 701-711, Dec., 1961 [received March, 1962]. 4 refs.

During a survey of the environmental histories of residents of North Wales and parts of Cheshire and Lancashire who died from cancer between 1952 and 1956, information was collected about the occupations followed, type of houses lived in, and sources of vegetables eaten over the 20 years preceding the onset of the disease. The deaths were classified in 6 groups according to the site of the primary growth—lung, stomach, oesophagus, intestine, rectum, and other—and the proportions in each were examined for each of four occupations. In Caernarvonshire and Merioneth the standardized mortality from cancer of the stomach in males was about twice the national rural average and the proportion of deaths attributed to this cause was much higher among men who had worked on farms or in quarries than among men in other occupations. In Denbighshire and Flintshire the standardized mortality from cancer of the stomach was about 1½ times the national rural average. In these counties the proportion of deaths attributed to this cause was substantially raised for men who had worked on farms and it was slightly raised for men who had worked in mines; there was no increase in quarry workers and it may be noted that the quarries in these counties are of sand or limestone and not of slate or igneous rock, as in Caernarvonshire. In Anglesey the mortality from cancer of the stomach was about 1.8 times the national rural average and the proportion of deaths was slightly raised in farm workers. In Cheshire the mortality from this condition was normal and there was no difference between the proportions in the various occupational groups.

Estimates are not available for the numbers of men employed in the types of occupation studied and an indirect method was used to estimate the age standardized rates in the various areas. These confirm that there is a higher mortality from cancer of the stomach among farm workers in the 5 Welsh counties, among quarry workers in Caernarvonshire, Merioneth, and Anglesey, and among miners in Denbighshire and Flintshire than among other workers. In contrast, there is a lower mortality from lung cancer among farm workers in Caernarvonshire, Merioneth, and Anglesey.

Similar data for married women failed to show an excess proportion of deaths attributed to cancer of the stomach among the wives of men in the occupational groups with high mortalities. It was also found that a history of having lived in a house with a vegetable garden and of having consumed green vegetables from it was not associated with an excess proportion of deaths from cancer of the stomach. It is suggested that the association between excessive incidence of cancer of the stomach in North Wales and certain soil characters may arise from direct contact with the soil in the course of daily work.

Richard Doll

426. Determination of the Maximum Concentration of Mercury in the Atmosphere. (Материалы к гигиеническому обоснованию предельно допустимой концентрации паров ртути в атмосферном воздухе)

V. N. KURNOSOV. *Гигиена и Санитария [Gig. i Sanit.]* 27, 7-15, Jan., 1962. 5 figs., 9 refs.

The concentration of mercury in the atmosphere around a factory emitting from 1.5 to 2.0 kg. of mercury vapour daily was determined at various points within a radius of 1,000 metres of the factory. Laboratory studies were then carried out on albino rats which were exposed to comparable concentrations and investigated for (1) the changes in conditioned-reflex activity, (2) the accumulation and distribution of mercury in the organs and tissues, and (3) the pathological changes, if any, in organs and tissues. Of the 5 groups of animals used, 4 were exposed to various concentrations of mercury vapour for 6½ hours daily for 9½ months, while the fifth served as a control group.

The investigations showed that exposure to mercury in a concentration of 0.002 to 0.008 mg. per cubic metre had a toxic effect on the functions of the higher divisions of the central nervous system, resulted in accumulation of mercury in the body, especially in the brain, and produced pathological changes in the internal organs, and that the degree of these toxic effects was proportional to the dose of mercury inhaled. Exposure to concentrations of mercury below 0.0003 mg. per c. metre (the existing maximum allowable concentration (M.A.C.) for atmospheric air) caused no visible toxic effects, and this limit may therefore be permitted to stand. A concentration of 0.01 mg. per c. metre (the existing M.A.C. for industrial premises in the U.S.S.R.) caused toxic changes under these experimental conditions, and one of 0.008 mg. per c. metre caused functional changes in the central nervous system. A review of the existing level of the M.A.C. for mercury vapour in the atmosphere of industrial premises is thus called for.

Basil Haigh

Forensic Medicine and Toxicology

427. The Significance of Blood in the Pleural Cavity Observed after Death

H. A. SHAPIRO and I. ROBERTSON. *Journal of Forensic Medicine* [J. *forens. Med.*] 9, 5-9, Jan.-March, 1962. 6 refs.

The authors criticize the medical evidence presented at a recent murder trial with regard to the significance of a roughly estimated amount of blood found in the pleural cavity of the victim, who had been shot through the chest. They point out that considerable haemorrhage into the pleural cavities may occur in life from chest wounds, especially if these involve the lung substance. Post-mortem bleeding, particularly from intercostal veins, may also account, they state, for variable but sometimes large amounts of blood being found in the chest at necropsy. In support of this last argument figures are produced from 6 cases of natural death in each of which a small stab wound of the chest was inflicted post mortem and the body then allowed to lie recumbent for periods varying from 7 to 30 minutes before the chest was opened by a technique recommended by Gonzales and his co-workers. The blood present in the appropriate pleural cavity was then measured accurately and the amounts found to vary from 50 to 1,000 ml.

The authors emphasize the need for care in evaluating the significance of blood found in the pleural cavities at necropsy in cases of wounding; they consider that the inferences which may properly be drawn from such a finding are extremely limited.

Gilbert Forbes

428. Aminoaciduria as a Manifestation of Renal Tubular Injury in Lead Intoxication and a Comparison with Patterns of Aminoaciduria Seen in Other Diseases

J. J. CHISOLM JR. *Journal of Pediatrics* [J. *Pediat.*] 60, 1-17, Jan., 1962. 7 figs., 36 refs.

The hypothesis that lead intoxication can give rise to Fanconi's syndrome was examined in patients at the Harriet Lane Home and the City Hospitals, Boston. The pattern of aminoaciduria found in lead poisoning was compared with that in other diseases which impair renal function. For this purpose 24-hour samples of urine were obtained from 23 children suffering from acute lead intoxication and 56 children and adults with various diseases in which one or more discrete renal tubular functions were known to be impaired. These were analysed for amino-acids by paper chromatography. Amino-acids in serum and sugars in serum and urine were analysed by the same method, of which the author gives details. Aspartic acid, glutamic acid, serine, glycine, threonine, alanine, and glutamine were separated on buffered filter paper chromatograms. Arginine, histidine, lysine, and tyrosine were separated on paper according to the technique of Block. Benedict's reagent was used to detect the presence of reducing sugars, and the total concentration of carbohydrate in urine was determined by the arsenomolybdate method of Nelson. The indole method of Dische was used for the quantitative determination of fructose in the presence of glucose. The urinary excretion of phosphorus was estimated by the method of Fiske and Subbarow, that of citrate by the method of

Natelson, Pincus, and Lugovoy, and that of creatinine by the Jaffe reaction. All other methods were standard ones. For control purposes urine from 10 healthy children aged 1 to 5 years was examined.

Of the 23 children with lead intoxication, 10 showed marked, 5 moderate, and 5 slight hyperaminoaciduria, while in 3 there was no increase in the excretion of amino-acids. Although the excretion of all amino-acids was increased, glutamine, alanine, histidine, threonine, and serine were present in the urine in the greatest concentrations. The quantities of these substances detectable increased with the severity of the illness. Serial paired specimens of serum and urine from 4 children with lead poisoning and 4 healthy children of similar ages were analysed to determine the origin of the hyperaminoaciduria in the former. The results, which were also compared with those in 2 patients in hepatic coma, suggested that the aminoaciduria of lead poisoning originates from impaired renal tubular reabsorption rather than from hyperaminoaciduria.

The amino-acid:creatinine excretion ratios determined in 5 patients were 5 to 40 times greater in the acute phase of lead poisoning than during recovery. Similar determinations in patients with vitamin-D deficiency and cystinosis were compared with these and the results are shown graphically. The disproportionate manner in which amino-acid excretion increases with lead poisoning suggests that lead inhibits some tubular mechanism common to their reabsorption.

Of the 23 patients examined, 10 with marked hyperaminoaciduria had reducing substances in the urine, and in 8 of these the concentration of phosphorus in serum was less than 3.5 mg. per 100 ml. on admission. Renal function returned to normal 8 weeks after treatment and normal patterns were observed one year later. The concentrations of phosphorus in the serum and reducing substances (glucose and fructose) in the urine both returned to normal within 2 weeks. The excretion of citrate was greatly increased in plumbism, although the level in the serum was within the normal range.

The pattern of amino-acid excretion in acute lead intoxication was compared with that in vitamin-D-deficiency rickets, cystine storage disease and other forms of the Fanconi syndrome, congenital renal tubular acidosis, parathyroid adenoma, and Luder-Sheldon syndrome. Although the total quantity of amino-acids excreted varied in this group, the relative concentrations in individual samples were similar to the proportions found in lead poisoning. The only difference was the time required for output to return to normal. In congenital renal tubular acidosis normal output was restored in 10 to 21 days after therapy, in lead poisoning, in 4 to 8 weeks, and in vitamin-D deficiency after several months.

The author concludes that acute lead intoxication does give rise to the triad of hyperaminoaciduria, glycosuria, and hypophosphataemia (Fanconi's syndrome). It is the result of proximal renal tubular damage. The occurrence of fructosuria and citraturia in lead poisoning differentiates it from other diseases causing this syndrome.

Anne Tothill

Anaesthetics

429. Central Sterile Supply of Endotracheal Tubes: the Effect of Autoclaving on the Life of Mineral Rubber Endotracheal Tubes

D. C. C. STARK and E. A. PASK. *Anaesthesia* [Anaesthesia] 17, 195-207, April, 1962. 9 figs.

In this study, carried out at King's College Medical School, Newcastle upon Tyne, 90 new No. 9 cuffed endotracheal tubes were cut to a standard length of 10 inches (25 cm.) and serially numbered in indelible ink. After cleaning, the tubes were packed and autoclaved. Half the tubes were treated in a downward displacement type of apparatus, subjected to 20 minutes of moderate vacuum, 35 minutes at a temperature of at least 121° C. at a pressure of approximately 20 lb. per sq. inch (1.4 kg. per sq. cm.) and then dried for 45 minutes. The other 45 tubes were sterilized in a modern high-vacuum autoclave having a high-vacuum phase of 29.2 in. (72.5 cm.) of mercury for 5 minutes and a sterilizing phase of 10 minutes at 130° C. and a pressure of 29 lb. per sq. inch (2 kg. per sq. cm.). The tubes were then dried for 5 minutes at a vacuum of 26 in. (65 cm.) of mercury. On removal from the autoclave all the tubes were allowed to cool to room temperature and then tested, after which they were washed, dried, and repacked. Each tube passed through the sequence 10 times.

The pressure-volume relationships of the unsupported cuff was measured and used as a gauge of the compliance of the rubber; the liability of the tube to kinking was also tested. Finally the tubes were examined after each test by "independent" anaesthetists. It was found that the tubes treated in the "old fashioned" sterilizer showed a decrease in elasticity of the cuffs, although these were still fit for use after 6 tests. Autoclaving in the high-vacuum machine had little effect on the elasticity of the cuffs even after 12 sterilizations. The pressure required to cause kinking of the tube fell more slowly in the high pressure vacuum treated tubes but the difference was not significant. These findings were confirmed by the "clinical" inspections. The authors recommend that if tubes are sterilized by autoclaving they should, for safety's sake, be discarded after being used 6 times.

Mark Swerdlow

430. Morphine Combined with Tetrahydroaminacrine for Postoperative Pain

B. R. SIMPSON, E. SEELYE, J. I. CLAYTON, and J. PARKHOUSE. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 95-101, Feb., 1962. 16 refs.

Standard doses of morphine were compared with double doses combined with THA [tetrahydroaminacrine] for the treatment of pain following abdominal and perineal surgery. Patients were assessed not only according to the amount of pain before and after treatment, but also according to their level of consciousness, ability to move and willingness to cough. The design of the trial is explained.

Statistical analysis of the results showed an improvement in level of consciousness as a result of using THA, but no obvious improvement in pain relief, movement or coughing from the associated larger doses of morphine. This corres-

ponded with the clinical impression that although patients were more alert after THA they were not markedly better off in other ways.—[Authors' summary.]

431. Blood Trichloroethylene Concentrations during Anaesthesia under Controlled Conditions

J. I. CLAYTON and J. PARKHOUSE. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 141-148, March, 1962. 4 figs., 13 refs.

Known concentrations of trichloroethylene were introduced into the lungs of human subjects during mechanical ventilation at constant respiratory rates and tidal volumes. Samples of arterial blood and peripheral venous blood from the antecubital fossa and the back of the hand were collected during anaesthesia and recovery. Trichloroethylene was extracted from these blood samples by the Conway micro-diffusion technique, and estimated by a Fujiwara-type reaction.

When 0.5% v/v trichloroethylene was administered with minute volumes of the order of 10 litres, arterial trichloroethylene concentrations were in the region of 6 to 7 mg. per 100 ml. Administration of 1% v/v trichloroethylene resulted in arterial concentrations of the order of 12 to 17 mg. per 100 ml. In slim subjects the trichloroethylene concentration in venous blood from the antecubital fossa began to approximate to that of arterial blood after about 30 minutes; in more obese subjects at least one hour of trichloroethylene administration was necessary before venous blood from the antecubital fossa showed even approximately the same trichloroethylene content as arterial blood. Venous blood collected from the back of the hand resembled arterial blood more closely and more rapidly. Comparison of the observed blood trichloroethylene concentrations with the solubility figures for trichloroethylene in blood indicated that during 2 to 3 hours of anaesthesia equilibrium within the body is by no means attained.—[Authors' summary.]

432. Alterations in Response to Somatic Pain Associated with Anaesthesia. X: Further Studies with Inhalation Agents

J. W. DUNDEE, R. M. NICHOLL, and G. W. BLACK. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 158-160, March, 1962. 1 fig., 9 refs.

The analgesic action of subanaesthetic concentrations of the inhalation agents in common use has been studied. Diethyl and methyl-n-propyl ether, nitrous oxide, cyclopropane, and trichloroethylene all showed analgesic activity, but halothane and halothane-ether azeotrope did not. Nitrous oxide, in concentrations not exceeding 50% is considered to be the analgesic of choice when it is important that consciousness should not be impaired.

It is suggested that the analgesic action of the inhalation agents may be related to the sympatho-adrenal response which they evoke.—[Authors' summary.]

433. New Frontiers in Anesthesiology

V. WHITEHEAD and A. S. KEATS. *Connecticut Medicine* [Conn. Med.] 26, 305-311, May, 1962. 10 refs.

Radiology

434. **Angiography or Pneumography? (A Comparative Study of 670 Supratentorial Tumours).** (Angiographie oder Pneumographie? (Vergleichende Untersuchungen bei 670 supratentoriellen Tumoren))

G. FRIEDMANN, W. KRENKEL, and W. TÖNNIS. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 181-200, Feb., 1962. 10 figs., 21 refs.

This study from the University Neurosurgical Clinic, Cologne, is based on the investigation of 670 cases of supratentorial brain tumour. In 118 cases examined by pneumography practically all the tumours were situated parasagittally and were causing insufficient displacement of the anterior cerebral or pericallosal artery to allow of a definite diagnosis. Of the 57 cases of occipital tumour, 20% required additional pneumography to make sure of the relationship to the tentorium.

The authors note that the necessity for the additional performance of pneumography may depend on the size or position of the tumour, its character, and the reaction of the surrounding tissue.

F. M. Abeles

435. **Aimed Filling of the Third Ventricle with Positive Contrast Agents.** (Gezielte Darstellung des dritten Ventrikels mit Kontrastmitteln)

M. NADIMI and G. SCHALTENBRAND. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 204-206, Feb., 1962. 4 figs., 12 refs.

In carrying out aimed filling of the third ventricle with positive contrast media, as performed at the University Neurological Clinic, Würzburg, stereotactic equipment is used to puncture the lateral ventricle as close to the foramen of Monro as possible. Thereafter 3 to 4 ml. of "pantopaque" is injected and made to flow into the third ventricle. A sharp fall in electrical resistance indicates the entry of the instrument into the ventricle.

F. M. Abeles

436. **Injuries to the Meningeal Vessels in Epidural Haematoma as Seen by Angiography.** (Die Verletzungen der Meningealgefäße beim Epiduralhämatom im Angiogramm)

P. HUBER. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 207-220, Feb., 1962. 7 figs., 8 refs.

Contrary to the views expressed by previous workers the present author, who writes from the University of Berne, has found that in cases of epidural haematoma tears in the meningeal vessels can be demonstrated fairly frequently provided that angiography is carried out within 6 hours of the injury and that the external or common carotid artery is injected. Later on, the haematoma tends to compress the torn artery and thus to make the tear invisible. The extravasation of contrast medium is seen in the shape of blobs or streaks near the injured artery and alters in shape but persists throughout the venous phase, though it is then less sharply delineated than in the earlier arterial phase.

F. M. Abeles

437. **The Azygos Vein Arch and Its Valvular Apparatus: Angiographic Observations**

G. TORI and G. F. GARUZI. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 235-247, Feb., 1962. 8 figs., 42 refs.

The changes which occur in the arch of the azygos vein in a variety of conditions have recently attracted increasing attention. Detailed observation of the anatomical variations and changes in a number of pathological conditions have been investigated at the Radiological Institute of Bologna University where 150 angiocardigrams and 100 per-osseous azygograms were studied.

The arch normally presents a downward and medial concavity. Superimposition of the two limbs on a postero-anterior film produces an oval shaped image. A rounded shadow is found when the arch is horizontal. The vein joins the superior vena cava on its posterior aspect and very rarely opens medially. Valves are almost always situated in the mid or posterior third of the arch and were never observed in the anterior third. There are usually 2 valves, one or 3 being less common. The valves were visualized by retrograde filling during angiocardiology, particularly in cases of lesions of the tricuspid valve, and produced a characteristic coffee-bean appearance on postero-anterior projection. If reflux does not occur into the azygos vein its junction with the superior vena cava can often be seen as a negative shadow, this being due to blood not containing contrast medium entering the superior vena cava.

D. E. Fletcher

438. **Dilatation of the Hemiazygos Veins in Superior Vena Caval Occlusion Simulating Mediastinal Tumor**

I. STEINBERG. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 248-257, Feb., 1962. 4 figs., 30 refs.

The author has studied 4 patients with superior vena caval obstruction seen at New York Hospital-Cornell Medical Center, New York. In all 4 cases radiography showed small rounded shadows projecting from the left upper mediastinum close to the aortic knuckle. By means of intravenous angiocardiology with 30% "urokon", a dilute medium being used so as not to exacerbate the existing venous thrombosis, these were shown to be due to dilatation of the hemiazygos vein. The author stresses that anticoagulant therapy is indicated for this condition rather than surgical intervention.

D. E. Fletcher

439. **The X-ray Diagnosis of Anomalies in the Lower Urinary Tract in Early Infancy.** (Die Röntgendiagnostik der Anomalien des unteren Harntrakts im frühen Kindesalter)

E. WILICH. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 245-259, Feb., 1962. 17 figs., 33 refs.

In this communication from the Central Röntgen Institute, Bremen, the author points out that for the diagnosis of anomalies of the lower urinary tract in infants three methods

of investigation are available, although, he suggests, all three should be preceded by routine intravenous pyelography. These are (1) cystography, for which any one of the modern sterile barium suspensions or alternatively 76% "urograffin" diluted 1 in 5 is suitable as contrast agent. Among the anomalies found here are enlarged bladder, pseudo-diverticulum of the bladder, and ureterocele. Of this last there are two forms: (a) orthotopic, occurring at the normal ureteric orifice, being more frequent in the older child and no different from that seen in the adult; and (b) ectopic, usually situated at a lower level and at the site of the attempted formation of a duplex ureter and kidney; in most cases the duplex kidney is insufficiently developed and does not function. The ectopic form is the more common in early infancy. The filling defect may be small enough to be invisible in the antero-posterior film, hence a lateral view is essential. The condition is serious, since the ureterocele can block either the normal ureteric orifice or the urethra, and it may even prolapse through the urethra.

(2) The second method is "expression urethrography". In very young children unable to micturate on command it is possible to fill the urethra by expressing urine from the bladder by external pressure; previous sedation is desirable and the child should be supine and oblique. To reduce the amount of radiation no grid is used. Here the urethrogram differs from the ordinary urethrogram in that the internal sphincter is not relaxed and the bladder neck therefore appears narrower. Conditions diagnosed by this method are: (a) stenosis of the neck of the bladder with sclerosis of the sphincter. This condition is more frequent in boys and it has been compared to congenital pyloric stenosis. The histology is variable, sometimes showing diminution of the glandular elements and an increase in the fibroelastic tissue—the fibroelastosis of Bodian. Urinary retention and eventual gross dilatation of the whole of the urinary drainage system follow. The characteristic x-ray finding is the posterior lip visible at the bladder neck caused by the enlarged sphincter. (b) Congenital urethral valves, occurring in males only. These "valves" are sail-like flaps which readily allow the entering cystoscope to pass and act as occluding valves only in the direction of the urinary flow. They are difficult to detect by the urethroscope, thus making x-ray diagnosis all the more important. The child's napkin may remain dry, but later there is paradoxical urinary retention with a constant trickle of urine. The valves may be unilateral or bilateral and proximal or distal to the colliculus seminalis. Dilatation of the urinary drainage system may be enormous and must not be thought to exist alone. (3) The third method, namely, retrograde urethrography, plays only a minor part in the investigation of congenital abnormalities of the urinary tract.

F. M. Abeles

440. Actinomycin D and Radiation Therapy

E. J. LIEBNER. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 94-105, Jan., 1962. 20 figs. 31 refs.

On the basis of increased skin erythema and the results of tissue culture studies it is suggested in this paper from the University of Illinois, Chicago, that actinomycin D has an additive effect on the response to radiotherapy. To obtain the full effect clinically actinomycin D should be administered, in a dose sufficient to produce some signs of toxicity, 2 to 4 hours before irradiation. If the drug is used alone only

temporary regression can be obtained; with combined therapy there is at present no indication that the total radiation doses should be lowered. Tumours in childhood have so far received the most attention, but a small study is being carried out on cases of carcinoma of the cervix uteri.

L. A. Elson

441. Clinical and Biologic Studies of Actinomycin D and Roentgen Irradiation

G. J. D'ANGIO. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 106-109, Jan., 1962. 3 figs., 21 refs.

In this paper from Harvard Medical School, Boston, it is pointed out that gross and microscopic radiation reactions in the skin of normal mice appear earlier and are more pronounced when actinomycin D is administered together with irradiation than when irradiation alone is given. Augmentation of radiation effects has also been demonstrated in transplanted animal tumours. In human beings skin and mucous membranes sometimes react earlier and more strongly to combined treatment than to radiotherapy alone, and actinomycin D alone may reactivate latent radiation effects in skin which has previously been irradiated but which has returned to normal.

Encouraging results with the combined therapy have been obtained in children with widespread metastases from Wilms's tumour.

L. A. Elson

442. Tumours of the Eye Treated by Radiotherapy

K. E. HALNAN. *Clinical Radiology* [Clin. Radiol.] 13, 19-28, Jan., 1962. 9 figs., 7 refs.

The author of this paper from the Christie Hospital and Holt Radium Institute, Manchester, states that malignant tumours of the eye and adnexae, other than basal and squamous-celled cancer of the lids, are very rare. The commonest are retinoblastoma in infants and malignant melanoma and lymphosarcoma in adults. Early cases of retinoblastoma may be treated with a radon gold tubing ring of appropriate size sewn on to the sclera. A dose of 6,000 r. is given in 7 days at 0.5 cm. If the lesion is close to the optic nerve a single-plane circular implant of radon gold seeds may be used. In this situation it may be impossible to place a ring in position. Of 8 patients treated by these methods, all are alive 4 to 10 years afterwards and 6 have vision. In late cases postoperative radiotherapy may be beneficial. Lymphosarcoma of the orbit carries a better prognosis than lymphosarcoma elsewhere in the body and requires a relatively limited treatment volume. The author states that of 17 patients with lymphoreticular disease confined to the orbit, 12 have survived 5 years. In malignant melanoma of the uveal tract 6 out of 13 patients have survived this length of time. A method of irradiating uniformly the whole of the orbit, by using a pair of oblique fields with megavoltage x rays and wedge filters is described.

M. Sutton

443. Effects of Radiation on the Lungs and Pulmonary Function in the Treatment of Carcinoma of the Bronchus. [Monograph, in English]

A. VOUTILAINEN, H. MÄHÖNEN, and A. O. HEINONEN. *Annales medicinae Internae Fenniae* [Ann. Med. Intern. Fenn.] 51, Suppl. 36, 1-19, 1962. 9 figs., 16 refs.

ABSTRACTS OF WORLD MEDICINE

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Pathology

444. **The Influence of Female Sex Hormones on the Course of Tuberculosis in Female Guinea-Pigs.** (Влияние женских половых гормонов на течение туберкулезного процесса у самок морских свинок)

T. I. BONAŠEVSKAJA. *Проблемы Эндокринологии и Гормонотерапии* [Probl. Endokr. Gormonoter.] 8, 64-69, March-April, 1962. 4 figs., 12 refs.

A relationship between exacerbations of tuberculous infection and functional changes in the sex glands (for example, in pregnancy) has been noted and commented upon since the middle of last century. In the present study the author investigated the effect of the administration of folliculin and of progesterone to female guinea-pigs which had been infected with a culture of *Mycobacterium tuberculosis* var. *bovis*-8 given subcutaneously. The animals were divided into three groups, of which one received 500 units of folliculin daily for 3 days before, and for one month after, infection, the second received 15 mg. of progesterone daily over a similar period, while the third group, which served as a control, were given 0.1 ml. of peach oil daily. Some animals in each group were killed one, 2, and 3 months after infection and the lungs, lymph nodes, liver, spleen, kidneys, and ovaries studied histologically.

Little difference in the clinical course of the tuberculous process was observed in the three groups, but the histological changes differed considerably, especially in the group receiving folliculin. In these animals there was an intense histiocytic reaction in the spleen, the interalveolar spaces of the lungs, and to a lesser extent in the liver, and a tendency to considerable fibroblastic reaction in the lymph nodes and spleen. In the other two groups these changes did not take place; here a tendency for the foci to coalesce and form necrotic masses was noted, this being especially marked in the group receiving progesterone. There was no apparent attempt at encapsulation.

L. Firman-Edwards

445. **Some Morphological Features of Latent Infection in Monkeys Inoculated with Attenuated Poliomyelitis Virus.** (Некоторые морфологические особенности латентной инфекции обезьян, вызванной аттенуированными штаммами вируса полиомиелита)

M. P. EROLOVA. *Вопросы Вирусологии* [Vop. Virus.] 7, 184-188, March-April, 1962. 3 figs., 21 refs.

In this experimental study 20 monkeys were inoculated, intracerebrally and 10 intraspinally with Sabin's attenuated poliomyelitis strains [no details of strain or strains given]. The animals were killed 21 to 28 days after infection and the central nervous system (C.N.S.) examined histologically; the C.N.S. of 15 healthy monkeys served as a control. None of the intracerebrally inoculated animals showed any clinical or morphological signs of poliomyelitis, but in 6

of the 10 intraspinally inoculated monkeys morphological evidence of poliomyelitis was present. Sections were stained with Nissl's haematoxylin-eosin, and histochemical stains such as Brascche's and Feulgen's were also used.

In 24 out of the 30 animals slight structural changes in the cytoplasm and nucleus, such as tigrolysis and ectopy, were observed, together with a marked disturbance of nucleic metabolism. The disturbance of nucleic metabolism was recognizable by the considerable reduction in the amount of ribonucleic acid, particularly in the central parts of the nerve cells, though very little in the peripheral parts. Distinct eosinophilic inclusion bodies in the nucleus were seen; these were present in 17 out of 20 intracerebrally and 7 out of 10 intraspinally inoculated monkeys. The changes described are interpreted as evidence of a latent infection in the C.N.S. with Sabin's attenuated poliomyelitis strains, and of their multiplication within the neurones.

K. Zinnemann

446. **Effect of Interferon on Vaccination in Volunteers**

A REPORT TO THE MEDICAL RESEARCH COUNCIL FROM THE SCIENTIFIC COMMITTEE ON INTERFERON. *Lancet* [Lancet] 1, 873-875, April 28, 1962. 4 refs.

A blind trial was conducted to assess whether topical interferon was able to protect against primary smallpox vaccination in human volunteers. Interferon was produced in influenza-infected trypsinized cultures of rhesus monkey kidney cells, and its potency assayed by inhibition of cytopathogenic effects caused by bovine enterovirus. Volunteers were inoculated intradermally with 0.1 ml. of interferon and with control fluid, and 24 hours later smallpox vaccination was carried out at these sites. The number of smallpox vaccination "takes" was significantly smaller at the sites of interferon inoculation, indicating its protective antiviral activity in man.

D. Geraint James

447. **The Partial Thromboplastin Time as a Screening Test for the Detection of Latent Bleeders**

S. W. NYE, J. B. GRAHAM, and K. M. BRINKHOUS. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 279-287, March, 1962. 24 refs.

It is suggested in this paper from the University of North Carolina that methods of detecting patients at risk from haemorrhage due to coagulation defects are not satisfactory. The results of simple tests of the clotting mechanism may be normal yet severe bleeding may occur at operation. In many patients more comprehensive investigation of coagulation is not practicable as a screening measure. The authors advocate the use of the partial thromboplastin-time test as a simple screening procedure. This is as simple to perform as the prothrombin-time test and consists simply

in estimating the clotting time of recalcified plasma in the presence of a lipid "partial" thromboplastin rather than the "complete" thromboplastin of the prothrombin-time test. They produce evidence that the partial thromboplastin time is sensitive to deficiencies of all plasma procoagulants except Factor VII. The test procedure is described in detail.

A. Brown

CHEMICAL PATHOLOGY

448. An Improved Dinitrosalicylic Acid Method for Determining Blood and Cerebrospinal Fluid Sugar Levels

A. F. MOHUN and I. J. Y. COOK. *Journal of Clinical Pathology* [*J. clin. Path.*] 15, 169-180; March, 1962. 3 figs., 11 refs.

The development of a standard technique for the estimation of "sugar" in blood and cerebrospinal fluid from the original chromatic method of Sumner (*J. biol. Chem.*, 1921, 47, 5) utilizing the reaction between glucose and 3:5-dinitrosalicylic acid in the presence of alkali and phenol is described. The present authors, working at the Archway Group and New End Laboratories (Archway Hospital Group), London, have developed an improved glucose-dinitrosalicylic reagent providing a straight-line relationship between the colour developed (measured at 550 m μ) and the glucose content. Full details of the derived standard technique and reagents are given. An extensive investigation is recorded in this paper of the different factors influencing the reactions and from which the eventual standard technique was formulated. "Results can be obtained in less than 10 minutes if required. The method is well suited to the estimation of random blood sugars and the handling of diabetic clinic requirements in hospital laboratories. The reagents are cheap, stable, and easily prepared. The results are very close to true glucose values in blood and cerebrospinal fluid. The technique . . . is sufficiently precise for all ordinary work." Simultaneous estimations were carried out with either the Hagedorn and Jensen technique or the glucose oxidase method of Marks and a very close approximation was obtained. Galactose, mannose, and fructose gave a colour development similar to that of glucose. Positive colour values were obtained from ascorbic acid and cysteine, but none from glutathione or urea. Certain antibiotics and procaine gave no colour reaction, but samples of tetracycline (containing ascorbic acid) and oxytetracycline produced some colour equivalent to that of glucose.

Harry Coke

449. Studies on Serum Haptoglobin: a Functional Inquiry

C. F. WHITTEN. *New England Journal of Medicine* [*New Engl. J. Med.*] 266, 529-534, March 15, 1962. 1 fig., 33 refs.

In 43 children with sickle-cell anaemia seen at the Receiving Hospital (Wayne State University College of Medicine), Detroit, the serum haptoglobin level, the urine and plasma haemoglobin values, and the haemosiderin content of the urine were determined quantitatively while the children were asymptomatic and free of infection, and when they had received no blood transfusion for at least 3 months. The same estimations were made on 10 of these children during the course of an infection, on 11 during a sickle-cell crisis of the infarctive type, and on 2 during a 3-month period when the haemoglobin levels were maintained by repeated transfusions of packed erythrocytes. Similar in-

vestigations were also made in 73 normal siblings of these patients as well as on 8 children with sickle-cell haemoglobin-C disease, 3 with non-spherocytic haemolytic anaemia, 3 with sickle-cell thalassaemia, and one with thalassaemia haemoglobin-C disease.

It was found that in the children with sickle-cell anaemia the plasma haemoglobin level was raised, haptoglobin was not present in the serum, and the urine contained haemosiderin but no haemoglobin. The author concludes that in these respects sickle-cell anaemia does not differ from other chronic haemolytic anaemias of more than mild severity. The sequence of events producing these findings he considers to be as follows: when haemolysis occurs intravascularly free haemoglobin appears in the plasma, where it combines with haptoglobin to form a complex which is rapidly eliminated from the circulation. If haemolysis persists the production of haptoglobin is exhausted and plasma haemoglobin is filtered out by the renal glomeruli into the tubular system. The proximal tubular cells have ability both to re-absorb haemoglobin and to metabolize it. Thus haemoglobinuria will occur only if the quantity of haemoglobin presented to the tubules exceeds their capacity to re-absorb and metabolize this protein. Though the upper limit of this capacity has not been precisely defined it seems to be quite high. The haemosiderin in the urine would then be the end-product of the catabolism of haemoglobin in the tubular epithelial cells. During the course of an infection, haptoglobin was restored in the children with sickle-cell anaemia; it is known that infection generally stimulates haptoglobin production. Since the absence of haptoglobin in the serum, haemoglobinaemia, and haemosiderinuria are relatively constant in children with sickle-cell anaemia, these factors might be assayed to determine the importance of the haptoglobins for protecting the kidneys against free haemoglobin. In 12 of the 43 children with sickle-cell anaemia the glomerular filtration-rate was determined within 18 months of the study, when it was found to range from 120 to 220 ml. per 1.73 square metre body surface and was therefore either normal or above normal. This finding is of considerable interest because it indicates that a certain amount of haemoglobin filtration through the glomeruli would appear not to damage the kidneys.

H. Lehmann

450. The D-Xylose Absorption Test

R. A. JOSKE and D. H. CURNOW. *Australasian Annals of Medicine* [*Aust. Ann. Med.*] 11, 4-14, Feb. [received May], 1962. 3 figs., 42 refs.

The literature on the metabolism of D-xylose in man is discussed in this paper from the Royal Perth Hospital and University of Western Australia, and the results of a number of D-xylose absorption tests are reported. The D-xylose level in the blood 2 hours after, and the amount of D-xylose excreted in the urine during the 5-hour period following, administration of 25 g. of D-xylose by mouth to 50 healthy subjects and to 186 patients with various pathological conditions were estimated. The healthy subjects had a blood level of 37.0 ± 7.2 mg. per 100 ml. after 2 hours and excreted 6.6 ± 1.4 g. (lower limit 3.8 g.) of D-xylose during the 5-hour period. Poor absorption of D-xylose was usually accompanied by other evidence of malabsorption; gross steatorrhoea could, however, occur with normal D-xylose absorption. Depression of D-xylose absorption was observed in sprue, adult coeliac disease, severe infective enteritis, and

other primary diseases of the small bowel, as well as in elderly patients with extensive vascular disease. The results of the D-xylose absorption test were variable after gastrectomy and in liver disease, the reticuloses, and rheumatoid arthritis. In pernicious anaemia, pancreatic disease, and diabetes mellitus the results were normal. Reduced D-xylose absorption was related to hypoalbuminaemia, but not to fat absorption or serum folic acid, vitamin-B₁₂, calcium, or potassium levels.

J. E. Page

451. Serum and Synovial Fluid Proteins in Arthritis

M. WILKINSON and B. S. JONES. *Annals of the Rheumatic Diseases* [Ann. rheum. Dis.] 21, 51-58, March, 1962. 12 refs.

The authors of this paper from Charing Cross and St. Bartholomew's Hospitals, London, have estimated electrophoretically the protein fractions in the serum and the synovial fluid from one or both knees, collected simultaneously from 50 patients suffering mainly from rheumatoid arthritis, degenerative joint disease, or traumatic synovitis. Total protein was estimated by the biuret reaction. Synovial fluids were incubated with hyaluronidase and then concentrated by dialysis against polyvinylpyrrolidone. In patients with rheumatoid arthritis the serum albumin level was lower and the α_2 - and γ -globulin levels were higher than in patients with degenerative joint disease. The values for all the protein fractions in synovial fluid were higher in rheumatoid arthritis than in degenerative joint disease. In nearly all the 38 specimens of synovial fluid from patients with rheumatoid arthritis the γ -globulin concentration was more than 1 g. per 100 ml. In degenerative joint disease, however, this level was strikingly lower. The synovial fluid:serum protein ratios in rheumatoid arthritis indicated increasing synovial permeability with the duration of disease, with an exceptionally high permeability for γ globulin. Examination of biopsy specimens of the synovium from some of the joints from which fluid had been taken suggested a correlation between the degree of lymphoid infiltration and the level of γ globulin in the synovial fluid. The authors favour the view that some of the γ globulin is produced by synovial cells. [Mellors *et al.* (Amer. J. Path., 1961, 39, 533; Abstr. Wld Med., 1962, 31, 245) have demonstrated rheumatoid factor in synovial plasma cells by a fluorescent technique.]

G. Loewi

452. Demethylchlortetracycline-Induced Fluorescence of Gastric Sediment. Use to Differentiate Benign and Malignant Gastric Lesions

J. E. BERK and S. M. KANTOR. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 997-1000, March 31, 1962. 14 refs.

In the investigation herein reported from Sinai Hospital and Wayne State University College of Medicine, Detroit, the authors demonstrated the presence of fluorescent material in gastric sediment after oral administration of demethylchlortetracycline. The drug was given in a dosage of 150 mg. 4 times a day for 5 consecutive days, a total of 3 g. After an interval of approximately 30 hours the overnight gastric contents were aspirated and the stomach then vigorously lavaged with the patient in each of 4 different positions. In each position 200 ml. of sterile saline was used for lavage and the stomach was massaged through the abdominal wall. The aspirated material was pooled, the pH adjusted where necessary to between 6 and 7 with 5% sodium bicarbonate,

and the material then centrifuged at 2,500 r.p.m. for 10 minutes. After the supernatant fluid was decanted the sediment was smeared on a Whatman No. 3 filter paper, allowed to dry completely, and then examined under ultraviolet light for bright yellow fluorescence.

In 8 cases of adenocarcinoma and one case of malignant lymphoma, which were subsequently confirmed histologically, the response to the test was positive. The result was also positive in 2 cases of gastric ulcer, histological examination demonstrating some "mucosal atypism". In 8 cases of other confirmed benign conditions the response was negative. Of 39 histologically unconfirmed cases of a variety of conditions, the result of the test was positive in 2; in at least one case a benign ulcer was thought to be present. The authors point out that the fluorescent substance is not present within the cancer cells, but is apparently contained within histiocytes and tumour stroma. In an addendum they report that of a further series of 48 patients the response to the test was positive in 8 out of 10 with malignant conditions and in 2 out of 35 with benign lesions of the stomach.

R. Salm

453. Clinical Evaluation of Glutamic Oxalacetic Transaminase Estimation: a Review of 550 Cases. [In English]

A. N. BHARGAVA, M. SINGH, and G. SINGH. *Zeitschrift für Immunitätsforschung und experimentelle Therapie* [Z. Immun.-Forsch.] 123, 1-12, March [received May], 1962. 30 refs.

MORBID ANATOMY AND CYTOLOGY

454. The Results of Exfoliative Cytology Studies in 50 Patients with Symptoms of Large Bowel Disorder

J. I. BURN and R. A. SELWOOD. *Gut* [Gut] 3, 32-37, March, 1962. 6 figs., 9 refs.

Experience of exfoliative cytology in the diagnosis of disorders of the large bowel is described from Hammersmith Hospital and the Postgraduate Medical School of London. Washings, free from all detritus, were obtained by means of a long colonic tube from 23 patients in whom malignant disease of the large bowel had been diagnosed and from 27 in whom no such diagnosis had been made. The technique of Raskin *et al.* (Dis. Colon Rect., 1959, 2, 46) was closely followed and in many cases a "millipore" filter was used to isolate cells. The results of cytological examination were positive in 19 of the cases of cancer. In the 4 cases in which a false negative result was obtained a filter was not used. One false positive result was recorded.

A. Wynn Williams

455. Hepatic Changes in Advanced Schistosomiasis

Z. A. ANDRADE, S. SANTANA JR., and E. RUBIN. *Gastroenterology* [Gastroenterology] 42, 393-400, April, 1962. 7 figs., 18 refs.

Necropsy specimens from 14 males and 3 females with hepato-splenic schistosomiasis were studied at Mount Sinai Hospital, New York. The youngest patient was 9 and the oldest 65 years old.

The weight of the livers varied from 900 to 3,700 g. The organ was always firmer than normal and showed focal fibrous thickening of the capsule. Occasionally a coarse macronodular appearance similar to postnecrotic cirrhosis

was seen. There was increased periportal fibrous tissue which, microscopically, varied in intensity, with loose oedematous fibrillar tissue adjacent to areas of hyalinized collagen. This tissue was well vascularized, and granulomata around ova of *Schistosoma mansoni* sometimes occluded the lumen of the vessels. The larger portal-vein branches showed fibrous intimal thickening and sometimes organizing thrombosis. Concentric intimal thickening with considerable narrowing of the lumen was seen in the branches of the hepatic artery in almost every case. From the enlarged portal spaces fine, long connective-tissue septa radiated into the parenchyma.

Granulomata around ova of *S. mansoni* were observed in every case, but their numbers varied considerably. They showed a zone of eosinophilic necrosis around the disintegrating ovum, focal epithelioid-cell accumulation, and peripheral concentric fibrosis. Other changes seen included features of postnecrotic cirrhosis (fibrous septa, collapse, and regenerative nodules), active chronic hepatitis with diffuse mononuclear-cell infiltration and "piecemeal" liver-cell necrosis, and also ischaemic changes.

The lack of correlation between hepatic inflammation and the degree of infestation with *S. mansoni* is puzzling. The authors suggest that the focal fibrotic changes may have been induced by "repeated ischemic insults tolerated for a long time, and by 'piecemeal necrosis', possibly an expression of a chronic immunologic response, either to schistosomal antigens or to liver-cell breakdown products, or to both".

H. Caplan

456. Cytological and Cytochemical Studies on the Liver in Infective Hepatitis

W. G. C. BEARCROFT and R. D. G. PEACHEY. *Journal of Pathology and Bacteriology* [J. Path. Bact.] 83, 373-381, 1962. 22 figs., 35 refs.

In the investigation herein described the authors set out to explore the liver cell changes in infective hepatitis and, especially, to seek evidence of virus synthesis. For this purpose 27 needle biopsy specimens of the liver were taken under local anaesthesia by the transpleural route from 23 African soldiers with infective hepatitis admitted to the Military Hospital, Yaba, Lagos, the specimens being obtained between 5 and 29 days after the onset of the illness. In 2 convalescent cases a second biopsy specimen was taken at 39 and 44 days. Control biopsy material was obtained from 6 healthy African volunteers and necropsy specimens from 4 patients who died between 4 and 8 days after the onset of the disease.

The earliest change was an enlargement and increased basophilia of the nucleolus. This was associated with a corresponding increase in nucleolar ribonucleoprotein (RNP). Later the RNP accumulated in the cytoplasm and might completely fill the cell. The nuclei and cytoplasm also became enlarged. There was no apparent increase in deoxyribonucleic acid (DNA). Most livers showed nuclei in various stages of mitosis and multinucleate cells were frequently seen. During the increase in RNP the mitochondria exhibited great variation in morphology and numbers. An inflammatory reaction and a variable amount of degeneration in the portal connective tissues were observed in all livers.

Necrosis of liver cells was widespread in all fatal cases and involved an estimated 50% to 60% of the parenchyma.

Usually the necrosis was most marked in the central portion of the lobules. The nucleoli and cytoplasm contained large quantities of RNP. Those cells which were undergoing degeneration showed reduced amounts of RNP. The nuclei were enlarged or distorted without any apparent change in DNA content. Comparison of these changes with those in the livers of monkeys infected with yellow fever suggested that the newly formed RNP might be concerned with virus synthesis.

The authors state that the possible presence of increased RNP in the connective tissue indicates that certain cells, notably fibroblasts, may support virus production.

A. W. H. Foxell

457. Electron-microscope Studies on the Liver in Infective Hepatitis

W. G. C. BEARCROFT. *Journal of Pathology and Bacteriology* [J. Path. Bact.] 83, 383-388, 1962. 13 figs., 17 refs.

This study from the Virus Research Unit, West African Council for Medical Research, Yaba, Lagos, is an extension of that described in Abstract 456. Portions of 14 of the 27 biopsy specimens from patients with infective hepatitis were studied under the electron microscope, portions of liver from 6 healthy controls also being examined.

In the specimens from cases of infective hepatitis large numbers of cytoplasmic granules were found which probably contained ribonucleoprotein. Their presence in large numbers near the nucleus suggested that they might have passed from the nucleoplasm through the pores in the nuclear membrane into the cytoplasmic matrix. In this situation groups of 6 to 12 granules appeared to aggregate to form rosettes. These rosettes were seen in 8 out of the 14 infected livers, but not in the 6 healthy livers. The author states that similar rosette formation is found in "yellow fever virus in monkey livers" and suggests that the rosettes may be mature particles of the virus of infective hepatitis. Further studies are, however, necessary before their true nature can be established.

A. W. H. Foxell

458. Pathogenesis of Postnecrotic Cirrhosis in Alcoholics

E. RUBIN, S. KRUS, and H. POPPER. *Archives of Pathology* [Arch. Path.] 73, 288-299, April, 1962. 13 figs., 21 refs.

This paper from the Mount Sinai Hospital, New York, presents evidence, based on the post-mortem examination of 342 livers, which supports a relationship between portal and postnecrotic cirrhosis. In most cases single blocks of liver tissue were stained by various methods described, including "luxol" fast blue for the detection of hyaline bodies. Post-necrotic cirrhosis was assessed by the presence of: (1) collapse characterized by fibrous areas free of liver cells but often containing proliferative bile ductules and approximated portal tracts; (2) multilobular nodules with more than 2 efferent veins; (3) variation in nodular size; and (4) variation in regenerative activity. Several cases of grossly misshapen liver, equivalent to nodular hyperplasia, were also noted, but are not discussed. The cases were subdivided according to the distribution of fat, fibrosis, and necrosis respectively, and the incidence and extent of these features were used to demonstrate consecutive stages of the same process. This is discussed and amplified by tables [and good photomicrographs].

Of 209 patients with an alcoholic history, 120 had portal cirrhosis and 89 postnecrotic cirrhosis. Among 81 non-

alcoholics there were 16 cases of portal cirrhosis and 65 of postnecrotic cirrhosis. The remaining 52 cases formed an indeterminate group in which postnecrotic cirrhosis prevailed. The following stages are described.

(1) Fatty liver with slight fibrosis and without necrosis. In most of these fat was present in more than half the liver cells. (2) Fatty cirrhosis with passive nodule formation. These nodules were formed by the extension and fusion of fibrous septa, dividing the parenchyma passively into nodules; the portal tracts were widened and showed inflammatory cell infiltration and bile ductule proliferation. (3) Fatty cirrhosis with necrosis, found exclusively in the livers of alcoholic subjects. Here there were foci of regenerating liver cells, inflammatory infiltration was intense, and there were frequent patches of centro-nodular ischaemic necrosis. (4) Fatty cirrhosis with collapse, which differed from the previous group mainly in the size and number of collapsed zones; here multilobular nodules were more frequent. (5) Portal cirrhosis with minimal fat. One-sixth of the cases in this group were from non-alcoholic subjects. Regeneration was marked by numerous nodules of regenerating liver cells with pronounced variation in nodule size. (6) Postnecrotic cirrhosis. Non-alcoholic subjects predominated in this class, but in more than one-third of the cases there was a history of alcoholism.

This study illustrates that postnecrotic cirrhosis and portal cirrhosis have features in common. The incidence of collapse, multilobular nodules, and variation in nodule size increases with the progression of portal cirrhosis. The number of hyaline bodies is at a peak during fatty cirrhosis with necrosis, but decreases as postnecrotic features increase. It is suggested that the probable course of events is portal cirrhosis $\rightarrow$ necrosis $\rightarrow$ collapse $\rightarrow$ regeneration, but other pathways leading to postnecrotic cirrhosis are also discussed.

F. Hillman

459. Progressive Muscular Dystrophy: the Histopathological Changes in Skeletal Muscle Obtained by Biopsy

G. W. PEARCE and J. N. WALTON. *Journal of Pathology and Bacteriology* [J. Path. Bact.] 83, 535-550, 1962. 12 figs., 23 refs.

In this report from the University of Durham and the Royal Victoria Infirmary, Newcastle upon Tyne, the authors review the muscle-biopsy findings in 68 cases of progressive muscular dystrophy (33 of Duchenne type, 19 of limb-girdle type, 1 of distal type, 4 of facio-scapulo-humeral type, and 11 cases of dystrophia myotonica) to discover whether histological findings can be correlated with the clinical types of muscular dystrophy. The changes were assessed quantitatively and are tabulated.

The histological appearances were unmistakably different in the myotonic and non-myotonic forms of progressive muscular dystrophy. It was, however, impossible to distinguish the individual non-myotonic types of progressive muscular dystrophy on histological grounds.

H. S. Schutta

460. Histopathological Features of Muscle in the Preclinical Stages of Muscular Dystrophy

C. M. PEARSON. *Brain* [Brain] 85, 109-120, March, 1962. 19 figs., 10 refs.

It has been shown that in children with muscular dystrophy a variety of enzymes normally found in muscle fibres are present in the serum. In a previous paper (New

Engl. J. Med., 1957, 256, 1069; Abstr. Wld Med., 1957, 22, 475) the author reported that the serum level of glutamic oxalacetic transaminase was high in most cases of childhood dystrophy. Further, in siblings of patients with muscular dystrophy, who later developed the disease, the serum level of this enzyme was also raised. This observation has been instrumental in uncovering early preclinical cases of muscular dystrophy.

At the University of California School of Medicine, Los Angeles, examination of muscle biopsy specimens from 3 members of one family with varying grades of preclinical or clinical dystrophy revealed a series of progressive changes in muscle fibres. In the earliest phase primary muscle fibre alterations and regeneration predominated. Significant connective-tissue invasion appeared somewhat later.

[For details the original paper should be consulted.]

R. Wyburn-Mason

461. Alveolar Fenestrae. Relationship to the Pathology and Pathogenesis of Pulmonary Emphysema

H. G. BOREN. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 328-344, March, 1962. 5 figs., bibliography.

The anatomical investigation of lungs obtained at necropsy from 41 males aged 39 to 84 years is described in this paper from the Veterans Administration Hospital, Houston, Texas. All the lungs showed gross evidence of emphysema, although only 9 of the 41 patients had clinical manifestations of this condition. The lungs were prepared for examination by inflation and fixation with formaldehyde fumes, and sections were examined both macroscopically and microscopically.

Emphysema was characterized by focal destructive lesions of the alveolar walls with large amounts of pigment and increased numbers of histiocytes and round cells. The degree of fibrosis was variable, but a constant finding was the presence of round or elliptical alveolar fenestrae. The number, form, location, and size of these fenestrae are described. It is postulated that they may be formed by direct damage to the alveolar wall associated with deposits of carbon and an inflammatory reaction; the damaged area is then sloughed out of the alveolar wall with the formation of fenestrae. Coalescence with adjacent fenestrae may occur.

The author argues that these lesions are not artefacts, but are one of the reliable criteria of emphysema; thus investigation of the pathogenesis of emphysema must deal with the mechanisms of formation of fenestrae. A. W. H. Foxell

462. Some Problems in the Pathology of the Thyroid Gland. (Некоторые вопросы патологии щитовидной железы)

V. M. ЛУПОВА. *Проблемы Эндокринологии и Гормонотерапии* [Probl. Endokr. Gormonoter.] 8, 80-87, March-April, 1962. 5 figs., 31 refs.

In introducing this histological study of 310 cases of nodular goitre the author emphasizes the frequency of malignant change in these tumours. Thus, in 17 patients (5.6%) in the series carcinoma of various types was found, while in another 33 (10.6%) signs of malignant change were present. The tendency was three times greater in solitary nodes than in multinodular glands. In view of the high degree of differentiation of the cells of thyroid carcinomata, very

careful study of serial sections of the nodes is essential to exclude malignancy. One of the danger signs is evidence of invasion of blood vessels, with thrombosis, degeneration of erythrocytes, and the presence of granules of haemosiderin and of epithelial cells in the lumen. Another danger sign is infiltration of the capsule of the node, while a further suspicious feature is the presence of solidified acini or tubular structure. Even in the absence of marked anaplasia such "adenomata" should in the author's view be regarded as potentially malignant.

L. Flrman-Edwards

IMMUNOPATHOLOGY

463. A Latex Particle Precipitation Test in the Diagnosis of Thyroid Disease

J. R. PHILP, D. M. WEIR, A. E. STUART, and W. J. IRVINE. *Journal of Clinical Pathology* [J. clin. Path.] 15, 148-152, March, 1962. 1 fig., 17 refs.

The authors, working at the University of Edinburgh, have investigated a capillary-tube modification of the latex particle agglutination test for antibodies to thyroglobulin. The degree of agglutination was roughly quantitated and the results are shown in the following table.

Diagnosis	Incidence of Degree of Agglutination (%)		
	None	1 to 2	3 to 4
Lymphadenoid goitre (111 sera)	29	24	46
Other thyroid disorders (113 sera)	65	28	7
Rheumatoid arthritis or systemic lupus erythematosus (57 sera)	72	25	4
Normal (70 sera)	100	0	0

If the results were recorded simply as positive or negative the test lacked specificity; thus 70% of Hashimoto sera gave a positive result, but so also did one-third of sera from patients with other types of thyroid disease and from cases of rheumatoid arthritis or systemic lupus erythematosus. If, however, only Grade 3 or 4 agglutination was scored as positive then specificity was considerably increased, as the table shows. The main drawback to this modification of the test was the difficulty in grading degrees of agglutination in capillary tubes.

[This modification of the latex particle agglutination test appears to be less useful than the simple slide test described by Rawstron and Farthing (see Abstract 464), which is much more rapid and more specific.] M. C. Berenbaum

464. A Comparison of Tests for Thyroglobulin Antibody

J. R. RAWSTRON and C. P. FARTHING. *Journal of Clinical Pathology* [J. clin. Path.] 15, 153-155, March, 1962. 1 fig., 16 refs.

In this study, reported from King's College Hospital, London, the authors have compared the sensitivity of the gel-diffusion, electro-precipitin, bentonite flocculation, tanned erythrocyte agglutination, and latex slide agglutination tests for antibody to thyroglobulin. Sera were obtained from 30 cases of Hashimoto's disease and 97 cases of other thyroid disorders (primary myxoedema, thyrotoxicosis, and non-toxic goitre). The results of the various tests were as shown in the table.

The gel-diffusion and the electro-precipitin tests were of equal sensitivity, and the results for these are therefore combined in the table. The latter test was preferable as

	Sera Reacting Positively (%)		
	Agar-diffusion or electro-precipitin	Latex slide test	Haemagglutination or bentonite flocculation
Hashimoto's disease	63	83	83
Other thyroid disorders	2	8	23

the results were obtained more quickly, and it gave in addition an electrophoretic pattern of the serum proteins. The latex slide test gave results within minutes and was of satisfactory specificity. The tanned erythrocyte agglutination and bentonite flocculation tests also equalled each other in sensitivity. However, they were time-consuming and, as the table shows, lacked specificity. The authors consequently recommend the electro-precipitin and the latex slide tests for use as diagnostic aids in the detection of Hashimoto's disease.

M. C. Berenbaum

465. An Immunological Cross-reaction between Group-A Streptococcal Cells and Human Heart Tissue

M. H. KAPLAN and M. MEYERERIAN. *Lancet* [Lancet] 1, 706-710, April 7, 1962. 5 figs., 19 refs.

The authors, from Western Reserve University School of Medicine, Cleveland, Ohio, describe the case of a boy who died of rheumatic carditis in whom gamma globulin was demonstrated, by immunofluorescence, bound to the ventricular myocardium. The same area stained with periodic-acid-Schiff reagent and was metachromatic. They suggest that the binding of gamma globulin and the myocardial failure might be due to antibody to human heart produced by an antigen of Group-A streptococci immunologically related to human heart. It was shown that rabbit-antiserum to the cell-wall of Group-A streptococci reacted with myofibres and vessel walls of the heart of both rheumatic and non-rheumatic subjects. Absorption with cell walls removed the activity of the serum, while cell protoplasm, protoplast membranes, and the medium on which the streptococci were grown were ineffective.

The rabbit antibody was demonstrated by complement fixation and immunofluorescence. The streptococcal antigen was partially purified, and was probably protein or conjugated to protein. An acid extract of 2 out of 7 strains of other Group-A streptococci tested was active.

The distribution of the bound gamma globulin suggested that it was related to the myocardial and vascular lesions of rheumatic fever. The relation to Aschoff bodies, valve lesions, subcutaneous nodules, and chorea was less obvious. The authors conclude that the demonstration of a cross-reaction between Group-A streptococci and heart muscle supports the hypothesis that tissue damage in rheumatic fever is due to cross-reacting antibody formed after exposure to Group-A streptococci.

[This paper is important and provides a reasonable explanation of the association of rheumatic fever and Group-A streptococcal infection.] G. L. Asherson

Microbiology and Parasitology

466. *Brucella* Infection in Regions of High Latitude. IV. Study of *Brucella* Cultures Isolated from Reindeer. (Бруцеллезная инфекция в районах Крайнего Севера. Сообщение IV. К изучению культур бруцелл, выделенных от северных оленей)

I. I. SERCHENKO and O. A. BAKAEVA. *Журнал Микробиологии, Эпидемиологии и Иммунологии* [Zh. Mikrobiol. (Mosk.)] 33, 69-76, March, 1962. 2 figs., 25 refs.

At the First Moscow Sechenov Medical Institute and the Gamaleya Institute of Epidemiology and Microbiology, Moscow, 16 strains of *Brucella* isolated from reindeer were investigated with regard to their differentiation from *Br. abortus*, *Br. melitensis*, and *Br. suis*. The reindeer strains form H₂S one to 2 days later than *Br. abortus* or *Br. suis*; they are inhibited by basic fuchsin, thionine, and pyronine, but not by methyl violet in a dilution of 1 in 200,000. Thus the dye test distinguishes reindeer strains very clearly from the other 3 *Brucella* species. Reindeer strains completely absorb both anti-*abortus* and anti-*melitensis* agglutinating sera, but are still agglutinated by anti-*abortus* serum absorbed with a *Br. melitensis* strain and by both anti-*abortus* and anti-*melitensis* sera absorbed with a *Br. abortus* strain. [No anti-reindeer serum was produced and tested in a similar way.]

Reindeer strains are less virulent for guinea-pigs than either *Br. abortus* or *Br. melitensis* strains as tested by establishing their minimal infecting doses and by the post-mortem recovery rate of the strains from the internal organs of experimental animals.

At present *Brucella* strains isolated from reindeer are to be regarded as a sub-type of *Br. melitensis*.

K. Zinnemann

467. Characteristics of *Brucella* Strains Isolated from Reindeer. (Характеристика бруцеллезных штаммов, выделенных от оленей)

A. F. PINGIN and O. S. PETUNOVA. *Журнал Микробиологии, Эпидемиологии и Иммунологии* [Zh. Mikrobiol. (Mosk.)] 33, 76-81, March, 1962. 8 refs.

At the Siberian and Far Eastern Plague Institute, Irkutsk, 41 *Brucella* strains isolated from the organs of male and female reindeer were compared with strains of *Br. abortus*, *Br. melitensis*, and *Br. suis*. Reindeer strains fermented arabinose in 22 to 30 days, whereas *Br. melitensis* does so in 4 to 5 days, and they form H₂S after 3 to 4 days and to a greater extent than *Br. abortus*, but in less quantity than *Br. suis*. Species-specific agglutinating sera showed a close resemblance of reindeer strains to *Br. melitensis*, agglutinating to the same titre or to one dilution below the titre, whereas there was a two-tube difference with *Br. abortus* serum. [If this study, as in the previous one (see Abstract 466), the desirability of producing a type-specific reindeer-strain serum and of carrying out cross-agglutination and absorption tests with the other *Brucella* species has been overlooked.] Growth of all *Brucella* strains from reindeer was inhibited by a 1 in 100,000 solution of methyl violet,

but not by 1 in 33,000 thionine or 1 in 50,000 basic fuchsin. Thus reindeer strains can be distinguished by means of the dye inhibition test. The virulence of reindeer strains for white mice was about 10 times greater than that of *Br. melitensis*.

The authors suggest that the reindeer strains represent a new *Brucella* species for which they propose the name *Br. rangiferis*, but in a footnote the editorial board of the journal dissociate themselves from this view on the grounds that not all the necessary criteria have been satisfied.

K. Zinnemann

468. Serologic Response of Children to Inactivated Measles Vaccine

C. H. CARTER, T. J. CONWAY, D. CORNFELD, D. G. IEZZONI, C. H. KEMPE, C. MOSCOVICI, L. W. RAUH, A. J. VIGNEC, and J. WARREN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 848-853, March 17, 1962. 2 figs., 17 refs.

In the investigation here reported from the University of Pennsylvania, Philadelphia, more than 5,000 children in various regions were given a formalin-inactivated measles vaccine containing alum, the aim of the study being to correlate the antibody levels evoked by vaccination with the results of tests of antigenic potency of the vaccine as assayed by measuring the immune responses in groups of guinea-pigs and monkeys. Although local tenderness with or without erythema at the site of vaccination was reported in several instances no significant general reactions were observed, save for fever of up to 101° F. (38.3° C.) in 4 infants on the evening after inoculation. Two types of vaccine were compared; the one, plain, was made from crude monkey-kidney tissue cultures, while the other, concentrated, was partially purified by chemical means. Both types were manufactured by a pharmaceutical firm from the Edmonston strain (non-attenuated) of measles virus, propagated in monkey-kidney tissue cultures.

Sera were available from 431 children who had received 3 injections of 0.5 ml. at intervals of one month. In neutralization tests sera from 233 (56%) of 425 individuals showed titres of 1:5 or more, indicating past infection with the virus. In those with no detectable antibody before vaccination the serological examination showed that the response obtained correlated well with the results of antigenic potency obtained in the guinea-pigs and monkeys. The plain vaccine evoked no response in 8 subjects, whereas the concentrated vaccine evoked a response in 171 out of 197 individuals with no detectable pre-vaccination antibody. The levels of antibody thus obtained were stated to be comparable to those obtained with live vaccine, but lower than those found after natural measles infection.

J. E. M. Whitehead

469. Observations on Acute Glomerulonephritis Associated with Impetigo

R. W. BLUMBERG and D. B. FELDMAN. *Journal of Pediatrics* [J. Pediat.] 60, 677-685, May, 1962. 5 figs., 16 refs.

Pharmacology and Therapeutics

470. Circulatory and Respiratory Effects of Guanethidine

R. ROKSETH, O. STORSTEIN, A. VOLL, A. M. ABRAHAMSEN, and J. OFSTAD. *British Heart Journal* [Br. Heart J.] 24, 195-200, March, 1962. 3 figs., 16 refs.

The haemodynamic and respiratory effects of guanethidine were studied during cardiac catheterization in 22 patients at the University Hospitals of Oslo and of Bergen, Norway. All but one of the patients had pulmonary hypertension, due in the majority to mitral stenosis. Guanethidine, 10 mg. in 2 ml. saline, was injected into the pulmonary artery through the cardiac catheter over a period of 2 minutes. The haemodynamic parameters, assessed before and after the injection, included systemic blood pressure (direct and indirect), pulmonary arterial and capillary pressure, total peripheral and pulmonary arterial resistance, heart rate, stroke volume, cardiac index, and cardiac output (Fick principle); respiratory factors studied included alveolar and lung ventilation, arterial oxygen and carbon dioxide tensions, oxygen consumption, and respiratory quotient. Pressure measurements were carried out at 2-minute intervals after injection, and cardiac output was again measured 15 to 18 minutes after injection.

There was a slight reduction in mean systemic, pulmonary arterial, and pulmonary capillary pressure, with an average reduction in cardiac output of 12% in 14 out of 17 patients. No significant change in pulmonary or peripheral vascular resistance occurred. Lung and alveolar ventilation was significantly reduced in 11 out of 15 patients, but the other respiratory indices were unchanged. Reference is made to an additional study of ventilatory response to the inhalation of 5% carbon dioxide in 10 patients before and after the intravenous injection of 10 mg. of guanethidine, when no significant change in response occurred.

The authors conclude, first, that the fall in systemic and pulmonary arterial pressure following guanethidine injection is probably due to a fall in cardiac output, and therefore pulmonary hypertension does not contraindicate guanethidine therapy. Secondly, they suggest that the decrease in ventilation is probably due to a direct action of guanethidine on either the motor neurone or the respiratory muscle itself, and does not involve the respiratory centre.

Gerald Sandler

471. The Local Effect of Glyceryl Trinitrate, Nitrite, Papaverine, and Atropine upon Coronary Vascular Resistance

E. D. FROHLICH and J. B. SCOTT. *American Heart Journal* [Amer. Heart J.] 63, 362-366, March, 1962. 1 fig., 10 refs.

This investigation was carried out at the U.S. Army Medical Research Laboratory, Fort Knox, Kentucky, on 18 mongrel dogs under pentobarbitone anaesthesia and subjected to cardiopulmonary by-pass. The aorta and pulmonary artery were clamped near the heart, and the coronary vessels supplied at a constant rate (average 92 ml. per minute) with arterial blood taken from the right femoral artery by a second pump, the pressure in the coronary arteries being recorded. Isotonic solutions of the various test drugs were then introduced at measured rates into the coronary per-

fusion and the effect on coronary arterial pressure measured. Since the inflow was constant an indication of coronary resistance was also obtained.

Evidence was obtained which indicated that glyceryl trinitrate, sodium nitrite, papaverine hydrochloride, and possibly atropine sulphate all produce coronary vasodilatation. On a weight basis glyceryl trinitrate was 90 times as active as the inorganic nitrite, and 6 times as active as papaverine. Electrocardiographic effects were also measured. Atropine in large dosage increased the heart rate, the Q-T interval, and the proportion of time spent by the ventricles in systole; the other three drugs were without significant effect on these parameters.

W. H. Horner Andrews

472. Hemodynamic Effects of Intravenously Administered Sodium Citrate

J. P. BUNKER, H. H. BENDIXEN, and A. J. MURPHY. *New England Journal of Medicine* [New Engl. J. Med.] 266, 372-377, Feb. 22, 1962. 2 figs., 26 refs.

In an attempt to separate the circulatory effects of citrate from other potentially adverse effects of massive transfusions of citrated blood, the haemodynamic effects of intravenous infusions of sodium citrate in lightly anaesthetized patients and a group of dogs have been studied at Massachusetts General Hospital (Harvard Medical School), Boston. To 6 patients who were undergoing operations for varicose veins under general anaesthesia sodium citrate was given intravenously and the effects studied. Similar experiments were carried out on 9 dogs. The haemodynamic measurements made included estimations of cardiac output and total peripheral resistance, while arterial and central venous blood pressures and the electrocardiogram (ECG) were recorded. The serum citrate, calcium, and magnesium levels were also determined.

In 5 of the 6 patients the maximum serum citrate concentrations varied from 2.4 to 4.1 millimols per litre (46 to 77 mg. per 100 ml.). The total serum calcium level remained essentially unchanged, but the calculated ionized calcium level fell from the normal value of 1 millimol to 0.5 millimol per litre. The mean arterial blood pressure fell by 16 to 30% and the pulse pressure by 37 to 50%. There was accompanying ECG evidence of hypocalcaemia—that is, prolongation of the corrected Q-T interval. Cardiac output fell in 3 patients, remained unaltered in one, and rose in one, while the work of the left ventricle declined markedly in these 5 patients. The sixth patient, who received the slowest infusion of citrate (3.7 per kg. body weight per minute) and in whom the maximum serum citrate level remained at approximately 1.6 millimols per litre, showed little change. Changes similar to those in the first 5 patients occurred in the dogs, and in these animals it was possible to carry out more detailed estimations. They showed that progressive increases in the serum citrate level led to further circulatory deterioration. The calculated serum ionized calcium level at the time of circulatory collapse or death varied from 0.55 to 0.16 millimol per litre. In both the dogs and the patients these changes could be corrected by

the injection of calcium chloride; and in one dog it was shown that calcium chloride given before the citrate protected against these haemodynamic changes. In 2 dogs there was a marked increase in sensitivity to citrate following a total sympathetic nerve block. It was also noted in the dogs that acetylcholinesterase given to 2 animals was also effective in reversing the haemodynamic effects. Noradrenaline was given to 3 dogs and in 2 produced improvement in the vascular collapse, but in the third animal there was a marked additional fall in blood pressure.

The experiments thus showed that circulatory depression occurs in both man and dog at approximately the same blood citrate levels, namely, 2.5 to 4 millimols per litre (47 to 75 mg. per 100 ml.). Critical circulatory depression or death occurred in the dogs at blood levels of 2.7 to 10 millimols per litre (50 to 190 mg. per 100 ml.), and at rates of infusion of citrate of 10 to 15 mg. per kg. body weight per minute. The circulatory depression in both species was manifested by hypotension, by variable changes in the cardiac output, and by narrowed pulse pressure, as well as by electrocardiographic evidence of hypocalcaemia. In their discussion the authors point out that to achieve serum citrate levels comparable to those in the present experiments it would be necessary to infuse multiple units of citrated blood at a very rapid rate—that is, about one unit (500 ml.) every 3 or 4 minutes to a patient weighing 70 kg. It is not unusual in war-time or in civilian disasters to transfuse at such speeds, but it is certainly less common in hospital practice. However, it is likely that tolerance to a raised serum citrate level and a low calcium level is less in the debilitated patient than in the healthy young patients studied. Further, it may be supposed that a patient with previously poor cardiac function or in haemorrhagic shock may be considerably less tolerant. It also seems likely that the effects of other factors such as hyperkalaemia, increased hydrogen ion concentration, and anaesthesia may share with citric acid in an additive effect in the aetiology of circulatory collapse.

R. F. Jennison

473. Angiotensin: Response of the Kidneys in Unilateral Renal-artery Stenosis

N. F. JONES and M. A. BARRACLOUGH. *Lancet* [*Lancet*] 1, 454-457, March 3, 1962. 4 figs., 8 refs.

In 2 hypertensive patients with unilateral renal-artery stenosis, angiotensin caused a fall in sodium excretion by the kidney distal to the stenosis, whereas it increased sodium excretion by the opposite kidney. These findings suggest that local renal changes determine the opposite effects of angiotensin on normal and hypertensive subjects. The significance of these observations is discussed.—[Authors' summary.]

474. Chlordiazepoxide ("Librium") and the Geriatric Patient

T. H. JONES. *Journal of the American Geriatrics Society* [*J. Amer. Geriat. Soc.*] 10, 259-263, March, 1962. 9 refs.

Oral chlordiazepoxide ("Librium") therapy was used in the treatment of 25 elderly patients in several nursing homes in the state of Washington supported by county or state funds. In addition to involutional syndromes, these patients had medical or surgical disorders, often in the terminal stages. Chlordiazepoxide was uniformly successful in relieving anxiety, tension and depression, and in resolving

emotional and behavioral crises, and even severe personality problems. Aside from dosage-related drowsiness and other slight side effects, there were no untoward reactions. This medication benefited patients with serious cardiac disorders, by preventing overexertion and exercising a general calming effect.

Chlordiazepoxide is a trustworthy and effective agent in the treatment of the geriatric patient ill enough to need nursing care.—[Author's summary.]

475. Action of "Tofranil" on Higher Nervous Activity: an Experimental Investigation. (О действии тофранила на высшую нервную деятельность по данным экспериментального исследования)

V. I. SAVČUK. *Журнал Невропатологии и Психиатрии* [*Zh. Nevropat. Psichiat.*] 62, 170-177, No. 2, 1962. 2 figs., 5 refs.

This paper from the Laboratory of Pathophysiology of Higher Nervous Activity, Moscow, reports an attempt to elucidate the mechanism of the antidepressive action of "tofranal" (imipramine) by a study of its influence on the processes of higher nervous activity in the normal dog and in dogs suffering from chronic experimental neurosis. In each dog a dynamic stereotype of conditioned motor responses (positive motor reflexes and differentiating responses) was produced. The stimuli for the positive motor reflexes were a bell and a siren. The differentiating stimuli consisted of uninterrupted light, interrupted light, and also metronomes beating at 120 and 60 beats per minute respectively (M_{120} and M_{60}). Reinforcement was by feeding. Each dog was assessed with regard to its type of higher nervous activity.

When doses of 1 to 5 mg. of tofranal per kg. body weight were given all or some of the following effects, depending to some extent on the type of higher nervous activity, were obtained in each dog within 30 minutes of giving the drug: maintenance of the positive reflexes at the upper limits of the control levels; constant or intermittent weakening of differentiating inhibition so that a motor response was often evoked by the second differentiating stimulus (interrupted light or M_{60}); abolition of periodic lapses in response to M_{120} ; a lengthening of the time needed for the extinction of the conditioned response to light; and an increase in motor activity and in the number of reactions occurring between signals. In a dose of 6 mg. per kg. the drug reduced the intensity of the conditioned reflexes and differentiation was less regularly disinhibited (more often preserved). Doses of 25 mg. per kg. produced a diminution or disappearance of some of the positive conditioned reflexes and no effect on differentiating inhibition; there was also general lifelessness and sleepiness at this level of dosage. By the simultaneous presentation of feeding and defensive unconditioned stimuli chronic "inhibitory neuroses" were produced. The symptoms, which included loss of conditioned reflexes, refusal of food, and erratic aggressive behaviour, were in no way benefited by a 10-day course of tofranal in a dose of 4 to 5 mg. per kg. 3 times per day.

The above results are thought to show that tofranal in optimum doses increases the process of excitation and diminishes the process of internal inhibition. This would explain its mode of action in depressive states, the basis of which the author believes to lie in a diffuse inhibitory process of the higher reaches of the brain.

G. P. McGovern

Chemotherapy

476. Sodium Nitrofurantoin Administered Intravenously: a Limited Study to Define Its Clinical Indication

A. HALLIDAY and E. JAWETZ. *New England Journal of Medicine* [New Engl. J. Med.] 266, 427-432, March 1, 1962. 3 figs., 7 refs.

Nitrofurantoin given by mouth is known to be effective as a urinary antibacterial agent, but it produces no demonstrable antibacterial activity in the serum. At the University of California Medical Center, Los Angeles, the sodium salt of the drug was given by intravenous infusion to 8 patients with urinary-tract infections in a dose of 180 to 720 mg. per day (1.1 to 6.84 g. in 6 to 10 days) in an effort to produce antibacterial levels in the serum and also to clear the infection. Drug levels of 60 to 240 μ g. per ml. were achieved in the urine, and 6 of the 8 patients showed dramatic subsidence of symptoms of urinary infection and suppression of bacteriuria. (The 2 failures were due to renal tubular acidosis and to resistant organisms respectively.)

Serum antibacterial activity, sought in 6 patients, was found in only one of them, and then only of a low order. There is therefore no evidence that intravenous sodium nitrofurantoin would be effective in systemic bacterial infections.

The drug is rapidly excreted after intravenous administration. There were no definite toxic effects, but a hepatotoxic action is a possibility, since the cephalin flocculation reaction changed from + to +++ in one patient.

The possible indications for administering sodium nitrofurantoin intravenously are said to be nausea and vomiting in a patient acutely ill with urinary-tract infection.

T. B. Begg

477. Teeth Pigmented by Tetracycline

I. S. WALLMAN and H. B. HILTON. *Lancet* [Lancet] 1, 827-829, April 21, 1962. 6 figs., 4 refs.

The incidence and nature of the pigmentation in the teeth of babies following tetracycline administration in the neonatal period were studied at the Princess Margaret Hospital for Children, Perth, Western Australia. The records of 64 babies, of whom 50 were traceable, given tetracycline and 8 children given oxytetracycline were studied. The site, severity, and distribution of the dental pigmentation were considered and correlated with the birth weight, gestational age, dosage, and duration of treatment.

Of the 50 babies given tetracycline, 46 had pigmentation of the teeth. This occurred in only one child given oxytetracycline. Neonatal jaundice developed in 8 babies given tetracycline, and in all these children dental pigmentation was marked. The pigmentation generally affected the gingival part of the incisors and the incisor part of the canines and molars, and when pigmentation was severe, deformity of the teeth occurred with faulty enamel formation. The pigment was yellow initially and became browner with age, probably due to oxidation, and was more marked when higher doses of tetracycline had been given. Oxytetracycline pigmentation differed from tetracycline pigmentation in being arranged in vertical lines instead of horizontal

lines. Fluorescence studies, absorption spectra, and histology indicated that the pigmentation was due to the tetracycline.

The authors briefly review the literature on tetracycline and pigmentation, and suggest that the deposition of the drug in bones and teeth may be due to its chelating properties and possibly to formation of a tetracycline-calcium orthophosphate complex. They conclude that oxytetracycline probably does not produce similar pigmentation and that tetracycline may be the commonest cause of enamel hypoplasia in young children. They surmise that permanent teeth may be affected similarly if tetracycline is given between 2 months and 2 years of age when calcification is occurring.

Gerald Sandler

478. Jaundice of the Newborn Due to Novobiocin

T. HARGREAVES and J. B. HOLTON. *Lancet* [Lancet] 1, 839, April 21, 1962. 1 fig., 5 refs.

The effect of novobiocin on bilirubin metabolism was investigated experimentally at the University of Leeds School of Medicine in order to clarify the production of neonatal jaundice by this drug. The conjugation of both bilirubin and *o*-aminophenol was studied in rat liver slices and homogenates and the effect of added novobiocin was determined, since conjugation of bilirubin is an essential step in excretion of the pigment in the human subject.

The rates of synthesis of both bilirubin glucuronide and *o*-aminophenol glucuronide were reduced by novobiocin in a concentration of 50 μ g. per ml. Further experiments with broken-cell preparations suggested that the inhibition of conjugation was due to a direct effect on the enzyme glucuronosyl transferase by the drug in concentrations attained by therapeutic administration.

The authors point out that newborn infants have a reduced level of glucuronosyl transferase and are therefore susceptible to novobiocin, whereas adults have an excess of this enzyme in the liver and are therefore much less likely to develop jaundice. They conclude that novobiocin should be used cautiously in the newborn.

Gerald Sandler

479. 2,6-Dimethoxyphenol [sic] Penicillin in Infants and Children: Preliminary Studies

P. A. DAY, W. OSBORN, H. L. WEINBERGER, W. MESIBOV, H. ROBIDOUX, and P. F. WEHRLE. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 102, 785-792, Dec., 1961. 17 refs.

The studies herein reported from the State University of New York Upstate Medical Center were designed to provide data regarding the absorption, toxicity, and efficacy of 2:6-dimethoxyphenyl penicillin (methicillin) in the treatment of staphylococcal infections in infants and children.

Absorption was studied in 11 children aged 6 to 12 years who had no evidence of infectious or renal disease. Intramuscular injections of 25 to 50 mg. of dimethoxyphenyl penicillin per kg. resulted in peak serum levels of the drug about half an hour afterwards. Serum levels fell rapidly and were below therapeutic levels in 3 to 4 hours. Nearly half

of the injected dose was excreted in the urine within 6 hours. There was no evidence of local or systemic toxicity.

The clinical response to dimethoxyphenyl penicillin was studied in 19 children (age range one day to 12 years) with staphylococcal infection. Coagulase-positive staphylococci had been isolated in 13 cases, and in the remaining 6 the organism had not been demonstrated. Administration was by intramuscular injection at 3- to 4-hourly intervals, the dose varying from 250 mg. to 3.3 g. a day. The drug was found to be equally effective in staphylococcal infections regardless of the sensitivity of the organism to benzylpenicillin.

A group of 249 normal newborn babies was also studied in order to determine the efficacy of dimethoxyphenyl penicillin in nursery staphylococcal infections. The results from single doses of 125 or 250 mg. of the drug provide evidence of a decrease in the frequency of colonization of staphylococci in nasal and umbilical areas when cultured on the 3rd day of life. This decreased incidence applied both to strains sensitive to and those resistant to benzylpenicillin. Since by the 4th day colonization rates were similar, it appears that for effective prophylaxis more than one dose at birth is needed.

It is suggested that dimethoxyphenyl penicillin "may be useful in the interruption of outbreaks of nursery-acquired staphylococcal disease and in the treatment of cases of staphylococcal disease".

G. Clayton

480. Environmental Antimicrobiosis in a Nursery: Qualified Success in Use of 2,6-Dimethoxyphenyl Penicillin During a Staphylococcal Outbreak

J. M. SUTHERLAND, R. M. HOTZ, F. E. RYTELL, V. R. DOWELL, M. L. COCHRAN, M. L. SHORT, and D. S. NEWMAN. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 102, 793-806, Dec., 1961. 5 figs., 41 refs.

A nursery outbreak of infection with penicillin-resistant staphylococci at Cincinnati General Hospital, where there were 4,300 deliveries in 1960, has permitted the testing of 2:6-dimethoxyphenyl penicillin (methicillin) as an agent for environmental antimicrobiosis. Previous data had suggested that resistance to 2:6-dimethoxyphenyl penicillin by coagulase-positive staphylococci would develop slowly and by other means than increased penicillinase production. The nurseries were sprayed every 6 hours for 22 days with 1.5 g. of 2:6-dimethoxyphenyl penicillin in 4.5 ml. of water, the nebulizer used giving a mean particle size of 0.54 μ . It was estimated that 20 μ g. of antibiotic would reach the respiratory tract of each infant every minute.

The results were encouraging in that there was a decrease in the proportion of infants and adults from whose nasopharynx staphylococci could be isolated; in one nursery colonization decreased from about 65% to 2 to 3%. The changes were less marked and occurred later in cord cultures. After the period of spraying, the infants became recolonized by organisms not encountered previously in the study; these included untypable coagulase-positive and penicillin-sensitive staphylococci as well as some Gram-negative organisms. There was no evidence of hypersensitivity in the nursery infants, and only 2 cases of possible mild sensitivity among the adults.

It is pointed out that the possibility of (1) dangerous colonization of a susceptible population, (2) penicillin sensitization of infants and adults, and (3) encouraging resistant

strains of staphylococci, must be weighed against the advantages to be gained before embarking upon environmental antimicrobiosis in this manner.

G. Clayton

481. Clinical Evaluation of 5-Methyl-3-phenyl-4-isoxazolyl Penicillin in Staphylococcal Infections

A. M. RUTENBURG, H. L. GREENBERG, S. S. LEVENSON, and F. B. SCHWEINBURG. *New England Journal of Medicine* [New Engl. J. Med.] 266, 755-759, April 12, 1962. 4 figs., 3 refs.

The authors, at Beth Israel Hospital, Boston, Massachusetts, have investigated the efficacy of 5-methyl-3-phenyl-4-isoxazolyl (M.P.I.) penicillin against staphylococci *in vitro* and in 50 patients with a variety of staphylococcal infections.

In the bacteriological investigations 98 cultures of staphylococci isolated from clinical sources were tested for sensitivity to M.P.I. penicillin, methicillin, and benzylpenicillin by a serial tube-dilution method. For 93 strains the minimum inhibitory concentration of M.P.I. penicillin varied between 0.18 and 0.78 μ g. per ml., and for the remainder between 0.78 and 3.1 μ g. per ml. The minimum inhibitory concentration of methicillin was between 0.18 and 6.2 μ g. per ml. All but 3 of the 98 strains were resistant to benzylpenicillin.

In the clinical study 50 patients with a variety of staphylococcal infections, 17 of whom had failed to respond to treatment with other antibiotics, were treated with M.P.I. penicillin. Staphylococci, most of which were coagulase-positive, were cultured from each patient. To 44 patients M.P.I. penicillin was given by mouth in a dose of 1.0 g. at 6-hourly intervals, and to 6 patients by intramuscular or intravenous injection in a dose of 0.5 or 1.0 g. every 6 hours. One patient developed a rash after 3 weeks of M.P.I. penicillin therapy, but no other side-effects were observed.

In 10 patients the results were classed as indeterminate because other methods of treatment may have played a part in the recovery. In the other 40 patients the results were considered to be good. No strains of staphylococci encountered in this study were resistant to M.P.I. penicillin.

Charles Rolland

482. Neurotoxic and Nephrotoxic Effects of Colistin in Patients with Renal Disease

E. WOLINSKY and J. D. HINES. *New England Journal of Medicine* [New Engl. J. Med.] 266, 759-762, April 12, 1962. 3 figs., 10 refs.

The authors, in this paper from the Metropolitan General Hospital, Cleveland, Ohio, describe toxic effects occurring during the treatment of 4 patients with colistin. Three of the patients were women with chronic urinary infections who were given colistin in doses of 3.1 to 4.8 mg. per kg. body weight per day. Each of them developed severe ataxia, which disappeared after the treatment was stopped. In 2 of these cases further impairment of renal function occurred during treatment.

The fourth patient was a boy of 13 with chronic otitis media who was inadvertently given 3 intramuscular injections each of 250 mg. of colistin (equivalent to 23 mg. per kg. per day). After the third injection severe ataxia developed with a steep rise in blood urea nitrogen level, but both these changes receded after the cessation of therapy.

The authors recommend that patients with impaired renal function should not receive colistin in doses exceeding 2 mg. per kg. body weight per day.

Charles Rolland

Infectious Diseases

483. **The Diagnostic Value of an Intradermal Test with the Allergen of Tsuverskalov in Dysentery in Children.** (Диагностическое значение внутрикожной пробы с аллергеном Цуверкалова при дизентерии у детей). Z. I. KARKOVA. *Voprosy OkhraNy Materinstva i Detsstva* [Vop. Okhranĭy Materin. Dets.] 7, 20-25, March, 1962. 8 refs.

The early diagnosis of dysentery in children showing symptoms of gastro-enteritis is clearly important, especially in atypical cases. In 1952 Tsuverskalov and Zaretskaja prepared a bacterial hydrolysate by means of prolonged oxygen hydrolysis of the proteins of the bacterial mass of Flexner's dysentery bacillus. This preparation has no toxic effects and in an intradermal test has proved of considerable value in diagnosing early dysentery. In this paper the author reports the results of the test in 314 children, most of them very young, who were divided into three groups: (1) 199 who were admitted with a diagnosis of dysentery; (2) 101 with acute gastro-enteritis of unknown aetiology; and (3) 14 who had no gastric symptoms but were suffering from other diseases such as Botkin's disease [infective hepatitis], measles, pertussis, and poliomyelitis.

Of the 199 children in Group 1, 85.9% gave a positive reaction to the test (area of the reaction 1x1 cm.). The author points out that the degree of reaction to the allergen of Flexner depends on the patient's age—the younger the child, the less the reaction, and vice versa; children under 3 months of age did not give a positive reaction. In all cases in which the diagnosis was established bacteriologically the reaction was positive, thus confirming that the test is specific. In 21% of the 101 cases in Group 2 dysentery was diagnosed on account of a positive reaction. No positive reactions were obtained in Group 3.

H. W. Swann

VIRUS DISEASES

484. **Viral Central Nervous System Disease: an Etiologic Study Conducted at the Los Angeles County General Hospital** E. H. LENNETTE, R. L. MAGOFFIN, and E. G. KNOUF. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 687-695, March 3, 1962. 2 figs., 23 refs.

The authors report the results of virological studies carried out on 511 patients with suspected viral disease of the central nervous system (C.N.S.) seen at the Los Angeles County General Hospital, California, in 1958. These included attempts to isolate poliomyelitis virus and Coxsackie or E.C.H.O. viruses from the stools and in some instances from the cerebrospinal fluid (C.S.F.), and determination of antibodies against poliomyelitis, Coxsackie virus Group B, Types 1 to 5, and the viruses of mumps, herpes simplex, Western equine encephalitis, and St. Louis encephalitis.

Although a widespread outbreak of aseptic meningitis occurred in Los Angeles during the study and was apparently attributable to Coxsackie B5 virus, this virus was encountered in only 38% of the 368 cases of aseptic meningitis investigated. Cases of infection with 20 different

enteroviruses, in addition to the viruses of mumps and herpes simplex, during the entire year were associated with cases of aseptic meningitis; in 31% of the patients with the latter disease, however, no instance of viral infection was established. The laboratory findings revealed several types of Coxsackie and E.C.H.O. viruses in 60 cases of clinical encephalitis, 5 of these cases being associated with Coxsackie B5 virus; in 33 (55%) of the cases no infective agent was demonstrated. The findings confirmed poliovirus infection in 26 (74%) of 35 non-vaccinated patients with clinical paralytic poliomyelitis, and in 3 (18%) of 17 patients who had received 3 doses of Salk vaccine. The viral agents associated with paralytic illness in 14% of the cases included Coxsackie virus Types B2, B3, B5, E.C.H.O. virus Type 9, and the mumps virus; 2 of these cases, attributable to Coxsackie B2 and B3 viruses respectively, showed significant residual paresis 2 months or longer after the onset of the disease.

In cases of disease of the C.N.S. occurring during the spring, the most frequently identified infective agent was the mumps virus; enterovirus infections, especially those associated with the Coxsackie B5 virus, increased markedly during June, attained a peak in late July and August, and declined during the autumn. The majority of the cases in each aetiological category occurred in children under 10 years of age, declined in number in adolescents and adults, and became rare after the age of 40 years; also, in all types of viral infections except herpes simplex males were affected more often than females, the male:female ratio ranging from 3:1 in poliomyelitis to 2:2 in mumps virus infections.

R. G. Meyer

485. **Enterovirus Survey in Children after Mass Vaccination with Live Attenuated Polioviruses** I. DÖMÖK, E. MOLNÁR, A. JANCsó, and M. DÁNIEL. *British Medical Journal* [Brit. med. J.] 1, 743-746, March 17, 1962. 4 figs., 14 refs.

In 1959 Hungary experienced an extensive epidemic of poliomyelitis in spite of the 2-year programme of compulsory immunization with Salk vaccine, and at the end of the epidemic young healthy children were still found to be heavily infected with poliovirus. From November, 1959, onwards, all children aged 3 months to 14 years were fed either 2 doses of a trivalent live attenuated poliovirus vaccine or separate doses of Types 1, 3, and 2 at monthly intervals in that order. In August, 1960, faecal samples were collected from 300 healthy vaccinated children aged 11 months to 4 years living in 10 different counties and were tested at the State Institute of Hygiene, Budapest, for enterovirus excretion, while samples of serum from 237 of them were tested for poliovirus antibodies.

Enteroviruses were being excreted by 79 of these children, but only two isolates proved to be polioviruses (Types 1 and 3) and both strains were found to be of rct/40- character, suggesting that they were vaccine strains. The commonest isolates were Coxsackie B4 and E.C.H.O. viruses Types 1 and 14. Neutralizing antibodies were demonstrated in 94.5%, 96.6%, and 94.4% of samples to Types 1, 2, and 3

of poliovirus respectively. Regardless of the virus type, the greatest number of negative results were found in children in the youngest age group (0 to 1 year). Those children who had received two doses of trivalent vaccine responded slightly better than those given monovalent vaccines.

In October, 1960, faecal samples were tested for enteroviruses from 1,010 children aged 3 to 8 months who had not been vaccinated against poliomyelitis and from 1,007 vaccinated children aged 9 to 23 months, the children being selected from all the 24 administrative districts of Hungary so as to give a proportion of about 20 per 100,000 of the population in each district. Enteroviruses were isolated from 142 (14.1%) of the unvaccinated and from 178 (17.7%) of the vaccinated children; no polioviruses were isolated from either group. Of the isolates, 236 proved to be E.C.H.O. viruses and 46 Cocksackie viruses, while 38 could not be identified. As in the August survey, E.C.H.O. viruses Types 1 and 14 and Cocksackie virus Type B4 were excreted most often. The peak enterovirus excretion was amongst the children aged between 13 and 18 months. Thus these surveys showed that while the circulation in Hungary of enteroviruses in general in 1960 was at least as extensive as in 1959, the polioviruses had practically disappeared. No poliovirus was isolated in 1960 from any of the 585 suspect cases of enterovirus infection, even from the 7 cases reported as poliomyelitis.

A. Ackroyd

486. **Small-scale Trial with Sabin Attenuated Type 1 Poliovirus Vaccine in a Semi-closed Community**
J. M. HOSKINS, D. HOBSON, V. UDALL, T. MADLAND, A. P. GOFFE, C. H. STUART-HARRIS, and E. G. HERZOG. *British Medical Journal* [Brit. med. J.] 1, 747-753, March 17, 1962. 4 figs., 20 refs.

In this small-scale trial, reported from the University of Sheffield, 3 of the 12 children, all under 4 years of age, in one ward of a long-stay orthopaedic hospital were given 1×10^6 TCD₅₀ of the living attenuated L Sc 2ab Type 1 poliovirus vaccine, and daily faecal specimens thereafter collected from all 12. The 3 children became infected and excreted virus for up to 32 days, often in considerable amounts (peak output, 1.1×10^6 plaque-forming units per g. of stools), but none of their associates became infected. On the 23rd day after the first feeding the other 9 children were fed the same dose of vaccine; 5 became infected and excreted virus for up to 33 days. No child became ill. Appreciable levels of antibody to the oral vaccine virus developed in all virus excretors, most of whom had had low or no antibody titres before vaccination. With one exception, all children with initially high antibody titres failed to become infected. Previous Salk vaccination *per se* appeared to make no difference to excretion.

When the excreted polioviruses were examined for their ability to grow at 40° C. and for their plaque-forming properties, using "monkey stable" cells, variations from the vaccine virus were observed, change in one characteristic being often, though not always, associated with variation in another characteristic. Although few viruses were found which grew at 40° C., they all produced plaques unlike those yielded by the vaccine virus. However, not all the faecal viruses which grew at 40° C. in primary plating yielded plaques on recultivation at the same temperature. The plaque size of the virus excreted by a single individual

varied, the variation being discontinuous when plotted against time, but both the large and the vaccine-like plaques from excreted poliovirus strains, when replated, were genetically stable.

Although after intraspinal inoculation of the vaccine virus into cynomolgus monkeys histological lesions were found in the cervical cord and brain of the animals, no neurotropic activity was detected after intrathalamic inoculation of massive doses; after the intrathalamic inoculation of excreted viruses from 4 of the 8 infected children 2 out of 50 monkeys became paralysed and histological lesions were demonstrable in the lumbar and cervical cord and brain. The 2 cases of clinical paralysis were caused by strains which showed evidence of growth at 40° C., but lesions throughout the central nervous system were evident in one of 3 monkeys inoculated with one excreted virus which was apparently similar to the vaccine virus.

A. Ackroyd

487. **An Outbreak of Febrile Illness and Pneumonia Associated with Respiratory Syncytial Virus Infection**

A. Z. KAPIKIAN, J. A. BELL, F. M. MASTROTA, K. M. JOHNSON, R. J. HUEBNER, and R. M. CHANOCK. *American Journal of Hygiene* [Amer. J. Hyg.] 74, 234-248, Nov., 1961. 2 figs., 10 refs.

Further evidence of the importance of respiratory syncytial (R.S.) virus as a pathogen for the respiratory tract of young children is presented in this study from the now famous children's institution, Junior Village, Washington, D.C. The group under study for 4 weeks in the spring of 1960 comprised 90 children aged from 6 months to 4 years. During this period 36 cases of pneumonia developed, compared with a normal incidence of 3 to 5 cases per month. R.S. virus was isolated from 24 children, but only during the latter half of the period after the need to avoid freezing the specimens before inoculation was recognized. A cross-sectional analysis at the peak of the outbreak showed a highly significant association between the isolation of R.S. virus and the occurrence of febrile pneumonia. Sera collected before and after the outbreak were examined by complement-fixation and neutralization tests. These showed that 73 (91%) of 80 children became infected by the virus during the period and that the presence of antibody before the outbreak did not influence the subsequent development of illness. In most patients the duration of fever was 4 days and coryza and cough were the main symptoms. The chief physical findings in the chest were patchily distributed fine crepitations. Radiological examination showed small areas of patchy infiltration in 3 of 5 patients, the appearances being normal in the remainder.

J. E. M. Whitehead

488. **The Role of Adenovirus in the Etiology of Infantile Pneumonia and Pneumonia Complicating Measles**

JEN KUEI-FANG, TAI YING, LIN YU-CH'UN, and WANG HUEI-YING. *Chinese Medical Journal* [Chin. med. J.] 81, 141-147, March, 1962. 6 figs., 14 refs.

In the winter of 1958 an epidemic of infantile pneumonia occurred in certain cities of North China. During the subsequent 3 years the authors of this paper from the Chinese Academy of Medical Sciences, Peking, studied the aetiology of infantile pneumonia and of pneumonia complicating measles. During the epidemic and from sporadic cases occurring since then, adenoviruses Types 3 and 7 were isolated. As many as 79 strains were cultured from 132

throat swabs from patients in whom viral pneumonia was diagnosed. In the period November to December, 1958, 13 out of 19 patients showed a fourfold rise in adenovirus complement-fixing (C.F.) antibody titre in convalescent sera. When lung tissue from fatal cases was examined adenovirus was detected in 15 out of 30 specimens in the period November to December, 1958, in 7 out of 18 between November, 1959, and May, 1960, and in 25 out of 38 cultured between November, 1960, and July, 1961. In one case Type-7 adenovirus was isolated from a suspension of thalamic tissue. Haemagglutination-inhibition tests carried out between November, 1960, and July, 1961, showed a fourfold rise in antibody titre in paired sera to 9 out of 10 Type-3 adenoviruses and to 14 out of 15 of Type 7.

Serological studies in 13 cases of post-measles pneumonia revealed a fourfold rise in adenovirus C.F. antibody titre in paired sera in 5 cases. In 1961 pulmonary tissue from 14 fatal cases of measles complicated by pneumonia during the eruptive stage yielded 6 strains of Type-7 adenovirus and one of Type 3. Some further studies showed that in human kidney tissue measles virus did not appear to interfere with the multiplication of Type-7 adenovirus.

The authors state that "concomitant infection by measles virus and adenovirus produced more severe symptoms, prolonged the clinical course and resulted in a higher mortality" and that "Type 3 and Type 7 adenoviruses may be considered to be the causative agents in some fatal cases of pneumonia complicating measles."

Kurt Schwarz

489. Attenuated Measles-virus Vaccine: Clinical, Antigenic, and Prophylactic Effects when Administered with Gamma Globulin

A. Z. KAPIKIAN, J. A. BELL, L. ROSEN, and R. G. JAMES. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 841-847, March 17, 1962. 2 figs., 17 refs.

The use of live attenuated measles virus vaccine has hitherto been complicated by the development of febrile reactions, sometimes resembling frank measles, in those vaccinated.

The study herein reported was carried out at the National Institute of Allergy and Infectious Diseases, Bethesda, Maryland, in an attempt to discover whether this disadvantage could be offset by the simultaneous administration of gamma globulin without affecting the serological response or degree of protection. For this purpose, 16 children in a welfare institution were given a single dose of 0.25 ml. of vaccine by subcutaneous injection followed immediately by an intramuscular injection of commercially available gamma globulin in the opposite arm in a dose of 0.02 ml. per lb. (0.044 ml. per kg.) body weight. As a control, 17 children, selected at random, received a similar dose of gamma globulin only. The vaccine virus strain was the Edmonston strain, which after numerous passages in tissue cultures of human origin had undergone 12 amniotic passages in hens' eggs, followed by 19 passages in chick embryo tissue cultures.

Nine vaccinated children and 7 controls developed febrile episodes with rectal temperatures of 100.6° F. (38.1° C.) or greater 4 to 14 days after inoculation. The duration and height of the pyrexia were greater in the vaccinated children than in the controls, but the symptoms such as rhinitis and pharyngitis were the same. None developed Koplik's spots or a rash. Antibody responses were measured by haemag-

glutination-inhibition (H.I.) tests; of 14 vaccinated children without antibody before vaccination 13 showed detectable antibody 3 to 6 weeks after inoculation. An outbreak of measles occurred just as the vaccinations were being completed. All of 12 controls who had received the gamma globulin at least 4 days before the onset of the first case developed the disease, in contrast to only one of 10 vaccinated children, and this one who developed measles was the only child who failed to develop antibody after vaccination. The presence of H.I. antibody was found to correlate well with resistance to the disease; of 31 children who were without antibody before the outbreak 29 developed measles, as compared with only one of 71 children with antibody.

J. E. M. Whitehead

490. Clinical, Virological, and Pathological Findings in a Fatal Case of Q Fever Endocarditis

I. C. FERGUSON, J. E. CRAIK, and N. R. GRIST. *Journal of Clinical Pathology* [J. clin. Path.] 15, 235-241, May, 1962. 8 figs., 16 refs.

491. Corticosteroids in the Treatment of Acute Hepatitis in Coma

R. KATZ, M. VELASCO, J. KLINGER, and H. ALESSANDRI. *Gastroenterology* [Gastroenterology] 42, 258-265, March, 1962. 4 figs., 10 refs.

Between 1940 and 1950 at the Hospital del Salvador, Santiago, Chile, the authors treated 16 patients in hepatic coma with intravenous infusions of glucose, but all died. Of these patients 7 were young adults in whom the coma occurred early in the course of the disease. From 1951 a new treatment regimen was therefore adopted. This consisted in the intravenous infusion of 150 to 200 g. of glucose with 500 mg. of tetracycline or oxytetracycline every 24 hours (care being taken to maintain a normal electrolyte balance), together with the intramuscular injection of corticosteroids, either cortisone, 500 mg. every 8 hours, or prednisolone, 100 mg. every 8 hours, or dexamethasone, 16 mg. every 6 hours. Soon after institution of this treatment it was observed that most of the recoveries took place in young males, so during the past 2 years female patients have received in addition 50 mg. of testosterone propionate daily.

Of 23 patients so treated 9 recovered, all 9 being young adults with coma of early onset. Patients who recovered regained consciousness in 12 hours to 7 days after the institution of treatment; all but one of those who died did so within 7 days. Extensive investigations of the value of hepatic function tests in assessing prognosis were carried out. The only indications found to be of any assistance were that an early rise in the plasma levels of the prothrombin complex and labile factor usually preceded a return of consciousness and recovery. The authors are not in a position to say positively which part of the treatment regimen described is the most effective in promoting recovery, since as it stands no part can reasonably be omitted. Reasons are presented for the inclusion of each of the drugs employed.

W. H. Horner Andrews

492. Prevention and Treatment of Viral Hepatitis

F. L. IBER and A. I. MENDELOFF. *Archives of Internal Medicine* [Arch. intern. Med.] 109, 310-322, March, 1962. Bibliography.

Tuberculosis

493. Tuberculosis Morbidity in a Controlled Trial of the Prophylactic Use of Isoniazid Among Household Contacts

S. H. FEREBEE and F. W. MOUNT. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 490-510, April, 1962. 5 figs., 12 refs.

Under the direction of the U.S. Public Health Service working in cooperation with 39 county health departments mainly in the southern States, extensive investigations were undertaken among household contacts of patients with recently reported active tuberculosis, the intention being to prevent or reduce the likelihood of infection by giving isoniazid prophylactically. In all, 25,512 contacts were examined, of whom 479 (a rate of 19 per 1,000) were found to be suffering from active tuberculosis, these including 136 adults with pulmonary tuberculosis and 343 children with radiological evidence of primary disease. The remaining 25,033 contacts who entered the trial were divided into two matched groups, of whom 12,439 were treated with isoniazid pills (dosage 5 mg. per kg. body weight daily) and 12,594 with placebo pills during one year.

Side-effects were not common, but slightly more frequent in the isoniazid group. It was estimated that some two-thirds of both groups took the pills regularly while 10% took them irregularly or only for a short time. The results showed that isoniazid reduced the incidence of tuberculosis among contacts as long as they took the pills. Thus the incidence of primary tuberculosis among children who were uninfected on entry to the trial was 16 cases in the placebo group and 5 in the isoniazid group; similarly of extrapulmonary tuberculosis there were 16 cases in the placebo group and 4 in the isoniazid group. In regard to adults, pulmonary tuberculosis was discovered in 62 in the placebo group and in only 4 in the isoniazid group. Although the trial was undertaken in the hope of reducing the risk of disease in subsequent years the results were disappointing in this respect. In the period following the completion of the trial there were 6 cases of primary disease and 2 of extrapulmonary and 17 of pulmonary disease in the placebo group, while in the isoniazid group there were 6 cases of primary disease and one of extrapulmonary and 10 of pulmonary tuberculosis. The authors emphasize the need for immediate examination of all household contacts of patients with active tuberculosis and for the continuation of further trials with isoniazid.

Franz Helmann

494. B.C.G. in Pulmonary Tuberculosis. Its Action on the Evolution of the Disease and on Tuberculin Allergy. (Le B.C.G. chez le tuberculeux pulmonaire. Son action sur l'évolution de la maladie et sur l'allergie tuberculinique)

R. COLLAS, J. PENINOU-CASTAING, G. MARISSAL, and J. SITE. *Poumon et le cœur* [Poumon] 18, 227-231, 1962. 1 fig., 4 refs.

In this study the results in 14 patients suffering from pulmonary tuberculosis who received 100 mg. of B.C.G. by mouth weekly for 2 years together with the usual antituberculous drugs were compared with those in 35 patients given a placebo of milk and water with the antibiotics. No beneficial effect from B.C.G. was noted. When given with the

antibiotics the B.C.G. appeared to be innocuous, but one case is reported in which a relapse occurred when, unknown to the physician, B.C.G. was taken without isoniazid. B.C.G. showed no effect on the evolution of the patients' allergy to tuberculin. A further group of 17 patients who were given 400 mg. of B.C.G. weekly for 6 months were compared with 30 patients treated with antibiotics alone. Again no greater favourable effect was noted in the B.C.G. group.

G. M. Little

495. Tuberculosis Occurring in Association with Corticosteroid Treatment

R. B. MAYFIELD. *Tubercle* [Tubercle (Lond.)] 43, 55-60, March [received May], 1962. 17 refs.

There is little doubt that most doctors believe that there is a distinct danger of inducing tuberculosis, or reactivating an old lesion, when corticosteroids are used for any length of time. This inquiry, reported from Bromsgrove General Hospital, Worcester, was conducted through the cooperation of 50 chest physicians throughout Britain and covered the years 1959 and 1960. It was mainly concerned with the total number of new cases of pulmonary tuberculosis in patients who had previously received steroids and the total number of reactivations in known tuberculous patients who had had corticosteroids, and then correlating these results with the total number of new cases seen during the same period.

There were 34 new cases of tuberculosis following corticosteroid therapy and 10 reactivations. Thus, if it is supposed that roughly 2.4 per 1,000 of the population were receiving corticosteroid therapy, the figures would indicate little relationship between such treatment and the incidence of new tuberculosis. Moreover, there was no evidence to suggest that the tuberculosis following corticosteroid therapy was a particularly serious form of the disease and, on the whole, the patients responded very satisfactorily to antituberculous drugs. The figure for the relapse rate—that is, 10—again indicates little relationship to previous corticosteroid therapy.

The author, however, still considers that patients who are to receive corticosteroids should have an x-ray examination of the chest, followed by further such examinations at suitable intervals. Old tuberculous lesions should be "covered" with antituberculous drugs.

Paul B. Woolley

496. The Use of Steroids in the Treatment of Tuberculous Empyema

A. J. IMARI. *Tubercle* [Tubercle (Lond.)] 43, 61-63, March [received May], 1962. 3 refs.

From the University of Baghdad comes this study, the primary object of which was "to investigate the practical value of steroids in the management of tuberculous empyema". The 24 male patients studied were divided into 2 groups, 12 receiving antituberculous drugs [no PAS!] with frequent aspiration for 12 weeks, and 12 the same treatment plus steroids in reducing doses over a period of 8 weeks. All 24 patients had active pulmonary tuberculosis on the

same side as the empyema, the other lung being normal. The sputum was positive in 20 cases.

The fluid disappeared rapidly in 9 of the steroid-treated group and 7 of the control group. The author gathered the impression that in the steroid-treated group the pus was thinner and therefore more easily aspirated; also subjective improvement was certainly more impressive in this group. [These figures are, of course, too small to be of any statistical value.]

Paul B. Woolley

497. Results, after Three to Six Months, of the Use of a Soluble Derivative of Ethionamide by the Intravenous Route in the Treatment of Pulmonary Tuberculosis. (Résultats, après trois à six mois de traitement, de l'utilisation d'un dérivé soluble de l'éthionamide par voie intraveineuse, dans la thérapeutique de la tuberculose pulmonaire)

A. TACQUET and V. MACQUET. *Revue de la tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 25, 1386-1404, Dec., 1961 [received April, 1962]. 4 figs., 15 refs.

The authors report an assessment of the value of intravenous therapy with soluble ethionamide in the treatment of 260 cases of bacteriologically proved pulmonary tuberculosis with cavitation and moderate to extensive spread of the disease. Of these cases 80 were available for analysis after 3 months and a further 17 after 6 months. Ethionamide was given in one daily infusion lasting 3 hours in a dose of either 0.5 or 0.75 g. in 500 ml. of serum-glucose; in addition a 0.5-g. suppository was given at night. No difference in the results was noted between the two dosages employed. In 94 cases ethionamide was combined with streptomycin, in 63 with cycloserine, and in 103 with isoniazid.

From their observations the authors conclude that ethionamide has its place in the treatment of pulmonary tuberculosis and that the combination with isoniazid gave the best results. The number of cases available for assessment at 6 months (17) was, however, too small to confirm this impression statistically. Drug resistance appeared to be delayed by 2 to 3 months when the intravenous route was employed, as compared with administration of ethionamide by mouth.

H. F. Reichenfeld

TUBERCULOUS MENINGITIS

498. Mental Retardation and Changes of Personality as Late Sequelae of Tuberculous Meningitis. (Retardatio mentalis und Persönlichkeitsveränderungen als Spätfolgen der Meningitis tuberculosa)

Z. ERDÖS and L. LIEBERMANN. *Annales paediatrici* [Ann. paediat. (Basel)] 198, 205-209, 1962. 6 refs.

The authors report from the University Paediatric Clinic, Budapest, that of 94 children who survived an attack of tuberculous meningitis 26 either became mentally retarded or had personality disorders. The majority were treated before isoniazid was available. Among the several methods of assessment the authors consider the Rorschach and the Szondi tests the most useful. They found that the personality of these children suffered severe psychological damage, there being narrowing of personality, decreased ability of adjustment, and decreased intelligence. Their affective and emotional life had become unstable and their resistance to stress effects had diminished. The whole

personality had become monotonous. In one-third of the cases the degree of mental-retardation was gross.

[Much may depend on the stage of the disease and the age of the patients when they come under treatment, as well as on the efficacy of treatment. In the abstractor's experience (*Paediatrics*, 1961, 28, 778) the overwhelming majority of survivors show no psychological or emotional residual symptoms and only 6% become severely retarded.]

John Lorber

499. Tuberculous Meningitis in Elderly Patients. (Туберкулезный менингит у лиц пожилого возраста)

L. I. GLONTI. *Проблемы Туберкулеза* [Probl. Tuberk.] 40, 31-35, No. 3, 1962. 11 refs.

At the Tuberculosis Institute, Tiflis, 789 patients with tuberculous meningitis were seen between 1948 and 1961; of these, 18 were over 50 years of age (an incidence of 2.3%, or 3.5% if the 285 patients under 18 years of age are omitted). Of these elderly patients 8 recovered and 10 died, necropsy being performed in 8 cases. The diagnosis of tuberculous was confirmed in all cases. In 2 instances tuberculous lesions were found in lymphatic and bronchial nodes, though they had not been visible on the radiographs. In 2 cases there were only generalized fibrotic changes in the lungs.

The author suggests that the cause of the meningitis in these cases is a dissemination of tubercle bacilli resulting from a flare-up of old tuberculous lesions which have been inactive for many years, and warns clinicians to be on the look-out for tuberculous meningitis in old people, pointing out that the initial stages can be very atypical. Thus in 2 cases the first clinical sign was a hemiparesis, which was taken for a cerebral arteriosclerosis, while in a further 2 the disease started with a high temperature but no headache at all. In another case the onset was purely a mental disturbance. As typhoid fever occurs fairly often in this region time was lost in excluding this disease. Early diagnosis is essential, as the patient's life may be saved by the early administration of antibiotics.

H. W. Swann

500. Ethionamide: Its Passage Into the Cerebrospinal Fluid in Man

I. E. HUGHES, H. SMITH, and P. O. KANE. *Lancet* [Lancet] 1, 616-617, March 24, 1962. 1 fig., 8 refs.

Ethionamide is one of the newer drugs potentially useful in the treatment of tuberculosis. Since it may have a place in the treatment of tuberculous meningitis, the authors, working at the Tuberculous Meningitis Unit of the United Oxford Hospitals, decided to study the passage of the drug into the cerebrospinal fluid (C.S.F.) after administration by mouth. This is important, as the drug cannot be given intrathecally. Two groups of subjects were studied, 6 patients with active tuberculous meningitis and 8 suffering from various other diseases but whose C.S.F. was otherwise normal.

Details are given of the techniques employed. It was found that in both groups the concentration of ethionamide in the C.S.F. rose to reach a peak at 3 hours after administration. Thereafter the levels in the serum and the C.S.F. were approximately equal. The authors conclude that ethionamide is a suitable "second-line" drug for the treatment of tuberculous meningitis or miliary tuberculosis.

John Lorber

Venereal Diseases

501. Cortisone in the Prevention of the Herxheimer Reaction in Early Syphilis

P. DE GRACIANSKY and C. GRUPPER. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 37, 247-251, Dec., 1961 [received Feb., 1962]. 2 figs., 22 refs.

This paper from the Hôpital Saint-Louis, Paris, is one of a series on the use of cortisone as an adjuvant to penicillin in the treatment of syphilis. The authors studied the incidence of the Herxheimer (febrile) reaction in 378 patients, 254 of whom (224 with early and 30 with late syphilis) received preventive steroid therapy in addition to penicillin; the remaining 124 patients (83 with early and 41 with late syphilis) received penicillin alone and served as controls. Various treatment schedules were used. It was found that a febrile Herxheimer reaction was more frequent in early than in late syphilis and that concurrent steroid therapy reduced the number of such reactions. *Leslie Watt*

502. The Immunolytic Test in Syphilis. (Il test di immunodisparizione (TPID) nella sifilide)

F. ALLEGRA, W. MARCHESELLI, R. SANTINI, and E. CSERMEY. *Rivista dell'Istituto sieroterapico italiano* [Riv. Ist. sieroter. ital.] 37, 12-27, Jan.-Feb. [received April], 1962. 27 refs.

Writing from the University Dermatological Clinic, Parma, the authors describe a serological test which is based on Pfeiffer's phenomenon and makes use of a treponemolytic antibody in syphilitic sera—the "Treponema pallidum immune disappearance" (T.P.I.D.) test. Nichols treponemata from rabbit orchitic testes (storable at -20° to -25° C.) are first incubated with the serum for 30 minutes at 37° C. and then injected intraperitoneally into a guinea-pig. Peritoneal fluid is withdrawn after 4 and 7 hours and the presence or absence of treponemes indicates a negative or positive result respectively. As killed treponemata are used, much of the difficulty of Nelson's treponemal immobilization (T.P.I.) test is avoided.

Of 151 syphilitic sera examined by the standard tests for syphilis (S.T.S.), the T.P.I.D. test, and/or the T.P.I. test, there was complete agreement between the T.P.I.D. and the T.P.I. and S.T.S. in 25. In another 73 cases there was agreement with the S.T.S. results; the T.P.I. test not having been performed on these. In 13 cases negative to the S.T.S., both the T.P.I. and T.P.I.D. tests were positive. In 12 cases there was disagreement between the T.P.I. and the T.P.I.D. tests and these cases are described in greater detail and discussed. Sera which gave a positive reaction to the S.T.S. and a negative reaction to the T.P.I. and T.P.I.D. tests were considered to be biological false positives. Tests of the sensitivity of the T.P.I.D. test carried out on sera in progressive dilutions showed that the T.P.I.D. test was slightly more sensitive than the Wassermann reaction.

The authors note that positivity of the T.P.I.D. test appears about 20 days after the primary chancre, that is, roughly about the same time as immobilisin appears. In their discussion they point out that the age, sex, or gravidity of the guinea-pigs does not matter, but that they should be about 200 to 250 g. in weight. The level of immobilizing

antibody is not parallel to the level of treponemolytic antibody. The result of the T.P.I.D. test was always clearly either positive or negative, a fact which the authors ascribe to the use of dilutions in geometric progression, adopted by them in conformity with French workers; dilutions in arithmetic progression may give transitional results. Storage of the serum does not affect the T.P.I.D. test; a repeatedly tested serum remained consistently positive for at least 6 weeks. This test is considered to be intermediate between the standard tests for syphilis and the T.P.I. test.

F. Hillman

503. Gonorrhoea Study—1960

BRITISH COOPERATIVE CLINICAL GROUP. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 38, 1-8, March, 1962.

This is a report of the fourth study of gonorrhoea by the British Cooperative Clinical Group. Information was provided by 161 clinics in Great Britain regarding the country of origin and age groups of 23,414 males and 6,253 females treated for gonorrhoea during 1960. Because of differing conditions, the situation in Scotland was considered separately from that of England and Wales. It was noted that gonorrhoea was more prevalent in the larger cities, with practically half the total occurring in London. Male patients born in the United Kingdom formed only 49.5% of those treated in England and Wales, but represented 93.3% of those treated in Scotland. West Indians constituted the next highest proportion, especially in the larger towns, and comparison with previous studies indicates that the proportion is steadily rising. Among females 83% were born in the United Kingdom, but comparison indicates a steady rise in the proportion of West Indian females treated in England and Wales. A significant increase in gonorrhoea has occurred in the younger age groups since the previous studies were made. *Leslie Watt*

504. T-strain Pleuropneumonia-like Organisms as One Cause of Non-gonococcal Urethritis

D. K. FORD, G. RASMUSSEN, and J. MINKEN. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 38, 22-25, March, 1962. 2 figs., 5 refs.

The investigation here described was undertaken at the University of British Columbia, Vancouver, to confirm earlier work elsewhere, and to determine the incidence of T-strain pleuropneumonia-like organisms (P.P.L.O.) in patients with non-gonococcal urethritis. Included in the study were 45 males with non-gonococcal urethritis (25 abacterial), 27 with acute gonorrhoea, and 55 controls without urethritis. Morphologically distinct colonies of T-strain P.P.L.O. were found in 60% of cases of non-gonococcal urethritis, with an incidence of 64% in abacterial cases. Epithelial-cell inclusions in Giemsa-stained scrapings correlated closely with the presence of T-strain P.P.L.O. in cultures. The incidence of T-strain P.P.L.O. in non-gonococcal urethritis was over twice that in any other group, yet the organisms were isolated from an appreciable number of control patients. This fact makes the significance of T-strain P.P.L.O. in non-gonococcal urethritis hard to evaluate from the data obtained in this study. *Leslie Watt*

Allergy

505. Influence of Adrenalectomy and Cortisol on Resistance of Mice to Histamine, Serotonin, Anaphylactic and Endotoxin Shocks

R. D. HIGGINBOTHAM. *Journal of Allergy [J. Allergy]* 33, 35-44, Jan.-Feb., 1962. 2 figs., 22 refs.

In this investigation reported from the University of Texas Medical Branch, Galveston, mice were sensitized to horse serum and subjected to bilateral adrenalectomy. Some of them received cortisol (hydrocortisone acetate) by the intraperitoneal route before the challenge. They were challenged intravenously with varying doses of histamine, serotonin, polymyxin B, compound 48/80, antigen, and staphylococcal endotoxin. Adrenalectomy considerably impaired the resistance to serotonin, endotoxin, and anaphylactic shock, while the resistance to histamine and histamine releasers was little impaired. Cortisol restored the resistance to serotonin, but was "less effective with regard to endotoxin and anaphylactic shock". Large doses of cortisol were necessary to increase the resistance to histamine.

H. Herxheimer

506. Post Mortem Differences in "Asthma" and in Chronic Bronchitis. [In English]

J. GOUGH. *Acta allergologica [Acta allerg. (Kbh.)]* 16, 391-399, 1961. 6 figs., 17 refs.

In coal-miners focal emphysema occurs around the deposits of coal-dust in the lungs, while in members of the general population who have emphysema there are two distinct patterns of affection, one (the more common type) being centrilobular and the other affecting the lung as a whole. The lungs of patients who had died in status asthmaticus, examined post mortem at the Welsh National School of Medicine, Cardiff, did not show destructive emphysema of the centrilobular type such as is commonly seen in cases of bronchitis. They were distended from simple over-expansion, with plugs of mucus in the bronchi and infiltration with eosinophils, the mucus being firmly adherent to the bronchial ciliated epithelium.

The author suggests that in places where bronchitis is common, as in the polluted atmosphere of London, cases of uncomplicated asthma such as occur in the clean air of Cardiff and Oxford may be rarer. He considers that the main factor in the causation of chronic bronchitis is environmental, including atmospheric pollution; smoking, and especially cigarette-smoking, is also an important causative factor.

A. W. Frankland

507. Asthma and Bronchitis with Emphysema. [In English]

D. A. WILLIAMS. *Acta allergologica [Acta allerg. (Kbh.)]* 16, 400-406, 1961. 1 ref.

The author of this paper from St. David's Hospital, Cardiff, begins by stating that he attempts to divide his wheezy patients into two groups according to whether they have (1) asthma or (2) bronchitis and emphysema. In discussing the differential diagnosis between the two conditions he points out that relatively fewer males than females die in status asthmaticus, and those who do usually have had

some emphysema. Some males who were asthmatic in young adult life ultimately died from bronchitis and emphysema with terminal cor pulmonale, but he has not seen such cardiac failure in a case of pure asthma. He considers that it is the male asthmatics who are heavy cigarette-smokers who develop lung damage. The female asthmatics among his patients were generally non-smokers (85%) or light smokers. While the males generally smoked much more than the females, the wheezy bronchitic males smoked more heavily and more frequently than normal subjects.

In asthma the number of eosinophils in the sputum is usually much increased, but this does not occur to such a marked degree in bronchitis with emphysema, and the author finds this helpful in distinguishing between the two conditions. To obtain an eosinophil count the patient is asked to cough sputum into a fixative (70% alcohol), and this is then embedded in paraffin and treated as a section and stained. With this method it was found that only 16% of patients with bronchitis had more than 10% of eosinophils in the sputum, whereas the figure for asthmatics was 87%.

A. W. Frankland

508. Precipitins, Reagins and Blocking Antibodies. [In English]

R. AUGUSTIN. *Acta allergologica [Acta allerg. (Kbh.)]* 16, 473-495, 1961. 7 figs., 37 refs.

Precipitins are not responsible for the immediate type of hypersensitivity, although they may occur in patients with mould allergy. They are, however, the cause of the Arthus-type reaction in the rabbit and also of the passive cutaneous anaphylaxis investigated by Ovary and his colleagues (*Progr. Allergy*, 1958, 5, 459). Precipitins are formed when pollens or moulds are injected into rabbits, and as rabbit antisera are capable of precipitating the bulk of skin reactivity of pollen extracts, gel-diffusion tests have been used to standardize the individual allergens of pollen. Reagins can be measured only by weal and flare reactions in the allergic skin or by transfer tests applied to normal skin. Infections with parasites produce reagin formation in all affected subjects, and reagin formation can, especially in depot treatment, be induced by injections of allergens in non-allergic subjects. Blocking antibodies produced by injection treatment, both in allergic and non-allergic subjects, are measured by various agglutinating procedures and are potentially precipitating antibodies. They can be characterized by immuno-electrophoresis. With this technique, gamma globulins can be shown to have a wide range of mobilities which react as far as the albumins. Reagins are found in the fast-gamma-globulin range, while the precipitins and blocking antibodies are found among the slow gamma globulins. Ultracentrifugal studies have indicated that reagins are, immunologically and by molecular weight, ordinary 7S gamma globulins like most other antibodies, and so far they have not been measured by any *in-vitro* tests. They may be associated with only one particular subunit of normal gamma globulin, but it is impossible to say whether they are functionally univalent or bivalent.

A. W. Frankland

Nutrition and Metabolism

509. Cutaneous Lesions in Kwashiorkor. A Histopathological and Histochemical Study

C. M. RANGAM, A. G. BHAGWAT, and J. C. GUPTA. *Indian Journal of Medical Research [Indian J. med. Res.]* 50, 184-190, March, 1962. 9 figs., 12 refs.

Skin biopsy was carried out on 31 children with typical skin lesions of kwashiorkor and on 10 subjects with healthy skin for comparison. The main histological features found in the patients with kwashiorkor were atrophy of the strata malpighii and basalis, disappearance of keratohyaline granules from the stratum granulosum, absence of melanin, and varying degrees of hyperkeratosis and parakeratosis. Histochemical tests showed a decrease in nucleoprotein, particularly ribonucleic acid, and an increase in alkaline phosphatase, which was concentrated in the stratum germinativum. Vitamin A could not be demonstrated. Vitamin C, determined chemically, was low in extracts of the biopsy material. Serum albumin concentration was less than 3 g. per 100 ml. Hypoproteinaemia occurred in most patients, and serum vitamin A and vitamin C levels were lowered. The skin lesions of kwashiorkor are considered to be due to multiple dietary deficiencies.

M. Lubran

510. Electrophoretic Pattern of Serum Proteins in Oedema Complicating Protein and Calorie Malnutrition in Adults

S. G. SRIKANTIA and C. M. JACOB. *Indian Journal of Medical Research [Indian J. med. Res.]* 50, 238-244, March, 1962. 12 refs.

The distribution of the electrophoretic components of the serum in nutritional oedema, and the effect of "nutritional rehabilitation" thereon, were studied in 20 patients at the Nutrition Research Laboratories of the Indian Council of Medical Research, Tarnaka, Hyderabad. Total serum protein levels averaged 5.6 g. per 100 ml. (normal 7.3 g. per 100 ml.); of this (as shown by agar-gel electrophoresis) albumin formed 53.2% (normal 65.8%) and γ globulin 25.5% (normal 15.7%). The levels of α_1 and α_2 globulin were slightly greater than normal, and β globulin was normal in amount. After treatment with 60 or 90 g. of protein daily for 4 weeks the serum total protein level rose to 6.5 g. per 100 ml., with albumin 64.1%, and the concentrations of globulin fractions became normal. The change was slow in the first 3 weeks, nearly all the restoration to normal occurring in the 4th week. Comparison with chemical methods showed the electrophoretic technique to overestimate albumin by about 17%, the error being greatest at low albumin concentrations.

M. Lubran

511. Effect of a Prudent Reducing Diet on the Serum Cholesterol of Overweight Middle-aged Men

N. JOLLIFFÉ, S. H. RINZLER, M. ARCHER, E. MASLANSKY, F. RUDENSEY, M. SIMON, and A. FAULKNER. *American Journal of Clinical Nutrition [Amer. J. clin. Nutr.]* 10, 200-211, March, 1962. 3 figs., 14 refs.

The study here reported from the New York Department of Health was undertaken to ascertain if a "prudent reducing diet", low in saturated fatty acids, was practicable as a

long-term measure and if it was effective in lowering the serum cholesterol level. In both respects, it was a success. The subjects were 211 volunteer overweight men aged 50 to 59 who were intended to lose 2 lb. (0.9 kg.) in weight per week; over a period of 10 weeks 111 of them lost at least 85% of the expected amount. The diet supplied an average of 1,600 Calories per day (range 1,350 to 2,000 Cal.) and contained about 33.5 g. of fat, 140 g. of protein, and 180 g. of carbohydrate, fat supplying 19% of the calories and saturated fatty acids only 7.8%. The ratio of polyunsaturated fatty acids to saturated fatty acids was only 1:0.6.

The average serum cholesterol level was 261 mg. per 100 ml. initially, but after 6 weeks on the diet it had fallen to 225 mg. per 100 ml. At 10 weeks the level was unchanged and it did not rise significantly thereafter, even in those patients whose diets were relaxed from the "prudent reducing diet" to a "prudent diet" when they had attained their ideal weight. In all, 74 men took the "prudent diet" for 6 months and 56 for at least one year. The study also demonstrated that it is unnecessary to give large supplements of vegetable oils in order to achieve and maintain serum cholesterol levels nearer to the normal.

T. B. Begg

512. Polyunsaturated Fatty Acids in the Lipids of the Atherosclerotic Femoral Artery. Changes after Corn Oil Supplementation of the Diet

P. BJÖRNTORP, L. O. HANSSON, and B. HOOD. *American Journal of Clinical Nutrition [Amer. J. clin. Nutr.]* 10, 217-224, March, 1962. 2 figs., 23 refs.

The authors report from the University of Gothenburg, Sweden, a study of 4 patients suffering from intermittent claudication in whom, for a few weeks or months before undergoing operation for surgical reconstruction of one or both femoral arteries, the "visible fat" in their diet was replaced by unsaturated fat, so that they were taking about 50 g. of polyunsaturated fatty acids, which accounted for about 50% of their total fat intake. At operation part of the arterial intima which had been in contact with blood flow was taken for detailed lipid analysis. In 2 of the patients parallel lipid studies were performed on the serum.

On an ordinary diet the fatty acid pattern was similar in the artery and in the serum in respect of the cholesterol ester fraction and the glyceride plus free fatty acid fraction. The phospholipids in the artery wall, however, showed lower values for polyunsaturated fatty acids; the fact that the molar ratio of fatty acids to lipid phosphorus was also low suggested that the arteries were richer than the serum in phospholipids, such as sphingomyelin, which have only one fatty acid per molecule, and usually a saturated or mono-unsaturated acid. When polyunsaturated fatty acids were given in the diet the concentrations of these acids in the cholesterol ester fraction and triglyceride plus free fatty acid fraction in the serum rose sharply and promptly, but in the artery the comparable rise was delayed. However, the close similarity of the lipid patterns in the serum and artery did indicate an exchange of lipids between serum and arterial wall.

T. B. Begg

513. **Lack of Correlation between Fatty Acid Patterns in Adipose Tissue and Amount of Coronary Arteriosclerosis**
R. F. SCOTT, A. S. DAOUD, A. GITTELSON, E. OPALKA, R. FLORENTIN, and F. GOODALE. *American Journal of Clinical Nutrition* [Amer. J. clin. Nutr.] 10, 250-256, March, 1962.

A study of the relationship between the fatty acid pattern in adipose tissue and the severity of coronary arteriosclerosis is reported from Albany Medical College, New York. Peri-umbilical fatty tissue was taken from 57 cases selected at random at necropsy, and after methylation the fatty acids of the tissue were analysed by gas chromatography; the degree of coronary arteriosclerosis was also assessed by measuring the thickness of the walls of the coronary arteries at various predetermined sites by means of special probes and callipers.

In these 57 subjects (28 male and 29 female ranging in age from 16 to 88 years) there was no correlation between the severity of coronary arteriosclerosis and the pattern of the fatty acids containing 12 to 18 carbon atoms. For example, there was no relationship between the proportion of linoleic acid or of total unsaturated fatty acids in adipose tissue and the occurrence of severe coronary arteriosclerosis or of myocardial infarction. Discussing the significance of these findings the authors point out that such negative results are of limited value and are conditioned by various uncontrolled factors, such as diet. T. B. Begg

514. **Long-term Weight Reduction in Cardiovascular Disease: Experiences with a Hypocaloric Food Mixture (Metrecal) in 78 Patients**

H. J. ROBERTS. *Journal of the American Geriatrics Society* [J. Amer. Geriat. Soc.] 10, 308-347, April, 1962. 6 figs., 34 refs.

Weight reduction is described in a group of 78 obese patients with cardiovascular disease, all of whom were seen in private practice and personally treated by the author on an out-patient basis. It was found that most of the patients lost more weight when they were receiving a regimen which included "metrecal" ["metrecal" in Britain] than when they were given various other regimens and diets. The advantages of this method of weight reduction and the inherent limitations are discussed. The author points out that the doctor "is not freed of the responsibility for indoctrinating his patients in proper diet".

[This article is vague and rambling and the study was uncontrolled.] A. G. Mullins

515. **Weight Gain and Serum Triglycerides in Normal Men**
M. J. ALBRINK, J. W. MEIGS, and M. A. GRANOFF. *New England Journal of Medicine* [New Engl. J. Med.] 266, 484-489, March 8, 1962. 6 figs., 19 refs.

Working at Yale University School of Medicine, the authors have determined the serum triglyceride levels in 215 healthy men aged 30 to 69 years who were divided into two groups according to the gain in weight during adult life. The weight-stable group, consisting of 78 men, had gained 10 lb. (4.5 kg.) or less after the age of 25, while the 137 weight gainers had increased their weight by more than 4.5 kg. It was found that the mean serum triglyceride level in the weight-stable group was 4.6 mEq. per litre compared with 7.1 mEq. per litre in the weight-gaining group, the difference being highly significant not only for the two groups as a whole, but also at each decade of age. Similar but

less significant differences were obtained for the serum cholesterol levels. In the weight-gaining group the highest triglyceride values were found, not in the most obese, but in those of average relative weight, the lowest values being seen in the leanest subjects. No relation between the serum triglyceride level and weight was found in the subjects in the weight-stable group.

A study of the importance of a family history of diabetes or coronary arterial disease showed that 76 men with such a family history in either a parent or a sibling had a higher mean serum triglyceride level than did the 163 with a negative family history (7.0 compared with 5.5 mEq. per litre). The lowest triglyceride values were seen in those with a negative family history and little or no weight gain, but even in this weight-stable group those with a positive family history had higher triglyceride levels. In the weight gainers with a negative family history, however, the serum triglyceride levels were higher than in the weight-stable men with a positive family history. Similar relations were noted in regard to serum cholesterol levels. In their discussion the authors point out that weight gain in young adults may be considered to be determined genetically, but weight gain after maturity may damage an organ or biochemical system not genetically equipped to deal with the excess weight. Lipaemia in subjects who gain weight is more often associated with coronary arterial disease than is essential hyperlipaemia of childhood, and appears to be closely related to carbohydrate lipaemia [although in this study no inquiry was made into the composition of diets]. A. Gordon Beckett

516. **Familial Mediterranean Fever: Plasma Protein Abnormalities, Low-fat Diet, and Possible Implications in Pathogenesis**

S. M. MELLINKOFF, R. W. SNODGRASS, A. D. SCHWABE, J. F. MEAD, H. E. WEIMER, and M. FRANKLAND. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 171-182, Feb., 1962. 7 figs., 18 refs.

The management of 25 patients with familial Mediterranean fever is described in this paper from the University of California, Los Angeles. The diagnosis was established on the basis of a careful study of the history and the exclusion of other causes of fever. The patients were given a diet with a maximum fat content of 20 g. a day. After a period of observation the basic low-fat diet was supplemented by the addition of 60 g. daily of either butter or corn oil. At a later stage the patients were allowed to take *ad libitum* long-chain unsaturated fats in the form of corn oil, peanuts, and sea foods.

The frequency of attacks of fever and pain was recorded during each of the diet periods. It was found that the low-fat diet and the diet of free unsaturated fats were accompanied by a reduction in the incidence of febrile paroxysms. Of the 5 patients taking the butter supplements 4 had paroxysms, which, however, did not start within the first 48 hours of taking the supplements. In the 9 patients given supplements of corn oil no paroxysms occurred.

The plasma lipid and serum lipoprotein levels, which were estimated in 6 patients, were not different from those in controls. The plasma fibrinogen and total serum glycoprotein levels were significantly higher in patients than in controls, but the authors could not correlate the number, severity, or duration of the attacks with the serum glycoprotein levels. Charles Rolland

Gastroenterology

517. A Retrospective Study of Etiological Factors in Cancer of the Mouth, Pharynx, and Larynx

W. R. VOGLER, J. W. LLOYD, and B. K. MILMORE. *Cancer [Cancer (Philad.)]* 15, 246-258, March-April, 1962. 4 figs., 24 refs.

This statistical study from the Robert Winship Memorial Clinic, Atlanta, Georgia, is based on a questionnaire filled in by all new adult patients and by patients with mouth cancer, both old and new, coming to the clinic over a 19-month period. Altogether 1,918 patients completed the questionnaire, giving information concerning possible aetiological factors in cancer of the oral cavity, pharynx, and larynx. The study group consisted of 333 patients with cancers at these sites, the remainder serving as controls.

Analysis showed that the following factors appeared to be of little aetiological significance: occupation, family history of cancer, syphilis, nutritional deficiencies, anaemia, and irritation by dentures and sharp or broken teeth. On the other hand there were definite indications that the use of tobacco other than in the form of cigarettes was the most striking extrinsic factor in the development of cancer of the oral cavity. In men tobacco-chewing was the form particularly implicated, and in women snuff-taking. This observation throws light on the fact that the incidence of cancer of the mouth and pharynx is considerably higher in white women in the south-eastern States than it is in other parts of the United States. In these States the habit of "snuff-dipping"—that is, holding snuff in the mouth against the buccal mucosa or under the tongue for varying periods—is prevalent among women. *R. B. Lucas*

518. Insulin Gastric Analysis: Technic and Interpretations

S. J. STEMPIEN. *American Journal of Digestive Diseases [Amer. J. dig. Dis.]* 7, 138-152, Feb., 1962. 7 figs., 14 refs.

In an attempt to standardize a more exacting technical procedure for determining the stimulating effect of insulin-induced hypoglycaemia on gastric secretion so that precise quantitative values can be established for interpretative purposes, the author has reinvestigated the insulin gastric analysis by performing the test in over 400 subjects at the Veterans Administration Hospital, Long Beach, California. In view of the fact that there is evidence that there may be a twofold gastric response to insulin stimulation, consisting of (1) an early phase transmitted from the anterior hypothalamus via the vagus, and (2) a delayed phase due to stimulation of the posterior hypothalamus and mediated by adrenal hormones, the test was modified so as to examine the secretory response for 4 hours after stimulation. The most suitable dose of insulin was found to be 11 units, and this was given intravenously. A gastro-duodenal tube was used for the collection of the specimens in 15-minute samples. Samples from the duodenum were included in the calculation of the HCl output if they had a pH of 2.5 or less, since this was taken to indicate considerable escape of gastric juice through the pylorus. The pH of the specimens was measured with a Beckman pH-meter and the amount of HCl calculated from these readings.

Of 30 normal young adult controls 24 (80%) secreted less than 1 mEq. of HCl per hour in the fasting state; secretion of 2 mEq. or more per hour was regarded as definite hypersecretion. In the majority of the controls acid secretion rose in the early phase after insulin but fell in the delayed phase, whereas patients with duodenal ulcer usually showed hypersecretion in the basic period and a sustained rise in acid secretion after stimulation for the full 4-hour period. After vagotomy secretion was depressed throughout the whole 4-hour period in those patients in whom vagotomy was thought to be complete. However, some paradoxical cases showed a high basal acid secretion and yet showed no further rise after stimulation. Examples are given of these various types of response.

[Unfortunately only sample cases are included in this paper and it is therefore impossible to judge the degree of overlap between the different groups, nor is it clear how many patients were tested in the different categories.]

T. D. Kellock

519. Medical Management of Chronic Gastric Ulcer

D. FERRIMAN. *Gut [Gut]* 3, 38-41, March, 1962. 18 refs.

This paper contains a report on 113 patients with chronic gastric ulcer given careful medical treatment under one physician at the North Middlesex Hospital, London. In 45 the ulcer healed and had not recurred 5 years later. The ulcer failed to heal in 43, while in 25 recurrence followed healing. From this and other reports it is estimated that approximately one-fifth of all chronic gastric ulcers may be non-recurring, and that reasonably satisfactory results after medical treatment may be expected in rather more than one-third of hospital patients. Adverse prognostic features included a long history, large size of the ulcer, and being of the male sex. *A. Wynn Williams*

520. The Diagnosis of Primary Tumours of the Duodenum

T. H. C. BARCLAY and H. P. KENT. *Gut [Gut]* 3, 49-59, March, 1962. 21 figs., 13 refs.

The authors describe the clinical and radiological features in 22 cases of malignant tumour of the duodenum (excluding lymphomata) seen in the clinics of the Saskatchewan Cancer Commission over a 22-year period. These cases represented 38% of all cases of malignant neoplasm of the small intestine and 0.38% of all those of malignant tumour of the gastro-intestinal tract. One patient had leiomyosarcoma and 2 had malignant carcinoid tumours; the remaining 19 patients (12 female and 7 male, most of whom were over 51 years of age) had primary adenocarcinoma of the duodenum. One tumour occurred in a patient with the Peutz-Jeghers syndrome. In 13 cases the tumour was below the ampulla of Vater.

The commonest symptom was loss of weight. Pain was never severe, and was related to eating in 5 patients. Vomiting was common, but the association with constipation was seen only in patients with an annular lesion. Jaundice developed in 10 cases, being intermittent in 8. The tumour was localized to the duodenum in 7 patients, and in 6 others

metastases had not spread beyond the regional lymph nodes. The tumour had metastasized in all patients with infiltrating and ulcerating lesions. There was no apparent relationship between the length of history and the presence of metastases.

The authors emphasize the importance in the diagnosis of carcinoma of the duodenum of demonstrating the duodenal loop distal to the ampulla of Vater, and note that the condition could be diagnosed preoperatively in patients in whom resection could be undertaken. *G. L. Asherson*

521. Clinical Remarks on Gastro-duodenal Ulcers Observed after the Age of 50 Years. (Remarques cliniques sur les ulcères gastro-duodénaux observés après l'âge de 50 ans) M. DEPARIS and G. MANIGAND. *Semaine des hôpitaux de Paris* [Sem. Hôp. Paris] 38, 845-847, March 8, 1962. 6 figs.

In a series of 100 patients with peptic ulcer studied at the Hôpital Bicêtre, Paris, 48 were over the age of 50. Of the 17 women in the series 13 were 50 and over. Again, out of 33 patients with an ulcer on the lesser curve of the stomach 21 were over 50, as were 21 out of 61 with duodenal ulcer, and all of 6 patients with pyloric ulcer. Many of the older patients had atypical symptoms, often without pain or relation to meals. Many ulcers were accompanied by bleeding (haematemesis in 27 cases and melaena in 14), especially in the 6th decade of life. In 20 cases bleeding was the presenting symptom. Of the 100 patients 13 were over 70 years of age. *Arnold Pines*

522. Hemigastrectomy-Vagotomy for Duodenal Ulcer: an Evaluation

D. A. FARMER, H. W. HARROWER, and R. H. SMITHWICK. *American Journal of Digestive Diseases* [Amer. J. dig. Dis.] 7, 195-208, March, 1962. 5 figs., 19 refs.

The authors report their experience, extending over some 14 years, of hemigastrectomy with vagotomy for duodenal ulcer, 114 patients having been operated on in this way at the Massachusetts Memorial Hospital, Boston, and 232 at the Veterans Administration Hospital, Providence, Rhode Island. They point out that after this procedure the incidence of recurrent ulceration is less and serious side-effects and poor results are fewer than after subtotal gastrectomy. The efficacy of the operation is judged by the absence of free acid afterwards, insulin being used to test the completeness of the vagotomy.

Approximately 80% of patients were achlorhydric after operation and none of these developed jejunal ulceration. In fact, only 3 patients out of a total of 336 had jejunal ulcers, and in all of them the vagotomy was considered to be incomplete. After re-operation by the thoracic route all 3 patients became achlorhydric and the ulcer healed. *Guy Blackburn*

523. The Effect of Nialamide on Endogenously and Exogenously Elevated Blood Ammonia Levels in Patients with Liver Disease

R. W. BEAL and C. R. B. BLACKBURN. *Australasian Annals of Medicine* [Aust. Ann. Med.] 11, 19-23, Feb. [received May], 1962. 3 figs., 23 refs.

The effect of nialamide (1-[2-(benzylcarbamylo)ethyl]-2-isonicotinoyl hydrazine) on high blood ammonia levels in 8 patients with liver disease and one with uraemia, and in 8 patients with liver disease whose blood ammonia level had been raised by continuous infusion of ammonium chloride,

has been studied at the University and Royal Prince Alfred Hospital, Sydney. In the first group of patients venous blood ammonia levels, measured before and after the intravenous injection of 100 mg. of nialamide, were found to be reduced to 18 to 75% of the initial levels. In the second group 100 mg. of nialamide was given intravenously after the arterial blood ammonia concentration had been raised at least 24 times by intravenous infusion of ammonium chloride (1.71 to 4.50 g.); nialamide again lowered the arterial blood ammonia level. In patients with hepatic coma or pre-coma the lowering of the arterial or venous blood ammonia levels did not lead to clinical improvement. *J. E. Page*

524. Autoimmunity in Liver Disease: Serologic Investigations with Clinical Correlations

M. GÖKÇEN. *Journal of Laboratory and Clinical Medicine* [J. Lab. clin. Med.] 59, 533-541, April, 1962. 28 refs.

The author, at the University of Minnesota Hospitals, Minneapolis, has investigated the autoimmune complement-fixation test of Gajdusek in various types of liver disease, primarily with the aim of evaluating its diagnostic significance. It was found that the reactivity of liver antigen depended on its source, and the antigens were accordingly divided into three types: (A) those from the livers of infants dying at or before birth; (B) those from cirrhotic livers; and (C) those from normal adult livers.

Serum from 4 cases of active primary biliary cirrhosis reacted with antigens A and C, and that from 7 of active post-necrotic cirrhosis with antigens B and C. Serum from 4 out of 10 cases of disseminated lupus erythematosus reacted with all three antigens. On the other hand there were only 2 reactive sera among 13 cases of acute viral hepatitis, and none in 45 cases of Laënnec's cirrhosis or 17 cases of extrahepatic obstructive jaundice.

It appears, therefore, that this test might be of assistance in the differential diagnosis of liver disease. *M. C. Berenbaum*

INTESTINES

525. Absorption of Folic Acid and D-Xylose as Tests of Small-intestinal Function

I. CHANARIN and M. C. BENNETT. *British Medical Journal* [Brit. med. J.] 1, 985-989, April 7, 1962. 5 figs., 22 refs.

At St. Mary's Hospital, London, the authors have studied the absorption and excretion of D-xylose and folic acid in 84 normal subjects, 61 patients with idiopathic steatorrhoea, and 22 patients with regional ileitis. The xylose (0.3 or 0.4 g. per kg. body weight) and folic acid (40 µg. per kg.) were given simultaneously to fasting subjects and the serum concentrations of these substances measured one hour and 2 hours later, while the urinary excretion of both substances during the first 6 hours after ingestion was also estimated.

The peak serum folic acid values enabled complete separation to be made between patients with idiopathic steatorrhoea and the controls, while all but 3 of the patients with regional ileitis had values below the lowest single value found in a normal subject. The urinary excretion of folic acid proved a much less reliable measure. The peak serum xylose concentration was rather more reliable than was urinary xylose excretion; it was abnormal in all patients

with steatorrhea, although in most of those with regional ileitis the figures were within the normal range. It is noted that 10% of patients given xylose developed acute diarrhoea within a few hours.

[There is much useful information in this paper, but other workers using the xylose excretion test may be deterred from undertaking serum folic acid estimations by the difficulties inherent in microbiological assays.] P. C. Reynell

526. Fulminant Ulcerative Colitis with Toxic Dilatation of the Colon: Medical and Surgical Management of Eleven Cases with Observations Regarding Etiology
F. W. SMITH, D. H. LAW, W. F. NICKEL JR., and M. H. SLEISSENGER. *Gastroenterology* [Gastroenterology] 42, 233-243, March, 1962. 1 fig., 37 refs.

The authors review 11 cases of acute fulminating ulcerative colitis seen at the New York Hospital-Cornell Medical Center; these all showed acute distension of the colon, which has been well recognized by others as being of grave prognostic import.

It is considered that the development of the acute dilatation of the colon was in the majority of cases precipitated by some aspect of treatment, narcotics, anticholinergic drugs, and barium enemas all being held responsible. It is pointed out that anything which impairs intestinal motility will increase distension, and that increased distension can easily produce necrosis of the bowel wall in these severely ill patients, this in turn leading to massive dilatation. On the other hand, it is not considered that corticosteroid treatment, which has been held responsible for this dilatation by other authors, does in fact increase the risk; on the contrary, it is maintained that corticosteroids have an important part to play in correcting a state of relative adrenal insufficiency produced by the effects of trauma, sepsis, and surgery, even in patients who have not previously received this type of treatment.

In discussing management of these cases it is suggested that rapid restoration of fluid and electrolyte balance and the administration of corticosteroids are the first steps. If recovery is not dramatic an early resort should be made to surgery, subtotal colectomy being the operation of choice. Of the 11 patients here considered, 8 recovered after surgery, one went into remission, and 2 died without operation.

T. D. Kellock

527. Fulminating Ulcerative Colitis with Marked Colonic Dilatation: a Clinicopathologic Study
G. T. MCINERNEY, W. G. SAUER, A. H. BAGGENSTOSS, and J. R. HODGSON. *Gastroenterology* [Gastroenterology] 42, 244-257, March, 1962. 7 figs., 13 refs.

During a 6-year period 1,230 patients with ulcerative colitis were seen at the Mayo Clinic. Thirty of these cases and 6 others seen later fulfilled the criteria for fulminating disease; all showed marked colonic dilatation, and these cases form the basis of this paper. There were 14 women and 22 men, ranging in age between 13 and 79 years. Sixteen patients were experiencing their first attack of the disease, 16 were in relapse, and the other 4 had the continuous type of disease. As would be expected, all the patients were very ill, fever, tachycardia, and mental confusion being prominent. Three of them were comatose on admission. All the patients had abdominal tenderness and the majority complained of cramping abdominal pains. It

was, however, noticed that radiographs often disclosed a greater degree of colonic dilatation than had been suspected on clinical examination. Radiologically, the transverse colon showed the maximal change in 35 cases; in 20 cases the mucosal surface and bowel wall had a "cobblestone" appearance, and in 16 cases the wall appeared to be thickened. Three patients received a barium enema while in the stage of colonic dilatation, and the condition of all 3 deteriorated after this examination.

Pathological examination was carried out on 13 specimens (8 surgical and 5 necropsy). Perforation was present in 10 specimens. In every specimen inflammation had spread throughout the whole of the bowel wall and involved the serosa, in marked contrast to the findings in 5 patients who survived the acute fulminating attack and later underwent resection of the colon; in these neither the muscle layers nor the serosa showed any inflammation.

Of the 36 cases, 28 were treated medically, with correction of electrolyte imbalance and administration of antibiotics; no corticosteroids were given in the majority of cases. Five of these patients died. One patient recovered from the acute dilatation, but shortly afterwards had a massive haemorrhage and required subtotal colectomy and ileostomy. The other 7 patients had either colectomy and ileostomy or caecostomy and/or colostomy with left hemicolectomy. Of these surgically treated patients 5 also died.

The authors conclude that the cause of the acute dilatation is obscure and that distal obstruction, hypokalaemia, and corticosteroid and antibiotic therapy are not important factors. They consider that medical treatment of this complication is indicated in the first place, in view of the successful outcome in patients so treated in this series.

[Other authorities would regard the poor results of surgery in this series to be due to overlong delay before operation, as shown by the very high incidence of perforation, a complication much better treated by surgical prevention than surgical "cure".] T. D. Kellock

528. Combined Steroid Therapy of Fulminating Ulcerative Colitis

S. G. F. MATTS. *British Medical Journal* [Brit. med. J.] 1, 1045-1048, April 14, 1962. 19 refs.

Twelve patients suffering from fulminating colitis were treated at the Royal Hospital, Wolverhampton, with a combination of ACTH intramuscularly and prednisolone enemas. All patients had high pyrexia (103° to 104° F. or 39.4° to 40° C.), severe toxæmia, and alterations in blood chemistry. Appropriate additional measures for correction of anaemia, shock, and electrolyte imbalance were used, and all patients were given penicillin and streptomycin in large doses. The prednisolone enemas (20-mg. strength) were given 8-hourly, and the soluble ACTH, 60 to 80 units 12-hourly by the intramuscular route. Nine of the patients recovered with this treatment, 2 recovered after surgery, and one died. The case histories of all 12 patients are given in detail.

The author suggests that the two steroids work better together than does either alone, and quotes evidence to support some synergistic action of the two combined; he recommends that they be tried in this way in all cases of fulminating ulcerative colitis, but abandoned in a few days if there is no improvement or any serious deterioration.

Thomas Hunt

Cardiovascular System

529. Lung Stiffness in States of Abnormal Pulmonary Blood Flow and Pressure

H. DAVIES, J. WILLIAMS, and P. WOOD. *British Heart Journal* [Brit. Heart J.] 24, 129-138, March, 1962. 9 figs., 18 refs.

At the Brompton and National Heart Hospitals, London, pulmonary function and compliance were measured in 20 patients with ventricular septal defect, 13 with atrial septal defect, and one with patent ductus arteriosus. Changes in pulmonary pressure were recorded by a differential manometer across a spirometer (giving mouth pressure) and an intra-oesophageal balloon. Corresponding changes in lung volume were recorded by the spirometer. Static lung compliance was calculated as the ratio of volume change to pressure change.

Results showed that lung compliance was abnormally low in those patients who had hyperkinetic pulmonary hypertension—that is, pulmonary arterial hypertension associated with increased pulmonary blood flow. Since such hypertension in congenital heart disease is related to chest deformity—namely, bilateral anterior bulging of the chest with indrawing of the lower ribs—the authors suggest that the deformity is caused by the stiff lungs which they demonstrated.

D. Goldman

530. Intracardiac Electrography in the Investigation of Congenital Heart Disease in Infancy and the Neonatal Period

H. WATSON. *British Heart Journal* [Brit. Heart J.] 24, 144-156, March, 1962. 14 figs., 3 refs.

The use of electrode-tipped cardiac catheters and the simultaneous recording of the intracardiac electrocardiogram along with the pressure pulse and scalar electrocardiogram during cardiac catheterization are shown to have several advantages in the investigation of congenital heart disease in infancy.

The atriogram (total electrical activity in an atrium) is useful in demonstrating the site of the catheter tip in various parts of the atria or the course of the tip as it is pulled back through defects at various sites in the atrial septum. It is particularly useful in locating the catheter tip when it is in the right atrial appendage. The ventriculogram (total electrical activity in a ventricle) may be useful in demonstrating the site of the catheter tip in various parts of the ventricles or in demonstrating its course on withdrawal through a ventricular septal defect. Routine recording of the intracardiac electrocardiogram is useful during selective angiocardiology. It may prevent the error of making an injection of opaque medium into the coronary sinus instead of into the right ventricle, since the electrocardiogram recorded in the coronary sinus is very characteristic, whereas the coronary sinus pressure pulse might be mistaken for a ventricular pattern. Also the presence of a contact current in the intracardiac electrocardiogram shows that the catheter tip is pressed against the ventricular wall, and it should be withdrawn until the ventriculogram is normal before injection is made, thereby preventing damage to the endocardium.

K. G. Lowe

531. Pharmacological Methods in the Phonocardiographic Diagnosis of Regurgitant Murmurs

J. ENDRYS and A. BARTOVÁ. *British Heart Journal* [Brit. Heart J.] 24, 207-213, March, 1962. 6 figs., 12 refs.

The value of pharmacological alteration of the pressure in the pulmonary and systemic circulations in the diagnosis of regurgitant murmurs was studied in 64 patients with incompetence of the various valves of the heart. Simultaneous phonocardiographic, electrocardiographic, and (in most cases) direct arterial pressure recordings were made before and after administration of 4 drugs—amyl nitrite, noradrenaline (20 to 40 μ g.), methoxamine (3 to 5 mg.), and serotonin (2.0 to 2.5 mg.), the first by inhalation and the last 3 by intravenous injection in 20 ml. of normal saline. In some cases direct right heart measurements were also made during cardiac catheterization. In all patients the diagnosis of valvular incompetence was made clinically, with or without confirmation by special investigations, such as cardiac catheterization, angiocardiology, dye dilution curves, and in some cases operation or necropsy.

An increase in peripheral resistance with increased pressure in the systemic circulation produced by noradrenaline and methoxamine increased the diastolic murmur of aortic incompetence and the systolic murmur of mitral incompetence; amyl nitrite, which reduced systemic pressure, reduced these murmurs from the left heart by reducing the amount of regurgitation. The increased pulmonary arterial pressure and resistance produced by serotonin and noradrenaline increased the murmurs of pulmonary incompetence and tricuspid incompetence arising in the right heart. In addition, amyl nitrite enhanced the systolic murmur of tricuspid incompetence when this was associated with mitral stenosis. Differentiation of regurgitant murmurs arising from the left and right heart could be made only by serotonin and methoxamine, which exert elective actions on the pulmonary and systemic circulations respectively.

The authors conclude that pharmacological alteration of regurgitant murmurs increases the accuracy of diagnosis.

Gerald Sandler

CONGENITAL HEART DISEASE

532. Diagnosis and Surgical Treatment of Aortopulmonary Fenestration

L. H. BOSHER JR. and C. M. MCCUE. *Circulation* [Circulation] 25, 456-462, March, 1962. 6 figs., 16 refs.

Five cases of aortopulmonary fenestration are described in this paper from the Medical College of Virginia, Richmond. It is pointed out that the clinical differentiation of this condition from other large left-to-right shunts (ventricular septal defect or patent ductus arteriosus) may be difficult. The murmur, which is frequently only systolic, is loudest in the third or fourth intercostal space. There is clinical, radiological, and electrocardiographic evidence of pulmonary hypertension. While cardiac catheterization will show a raised oxygen saturation in the pulmonary artery, a definite diagnosis cannot be made unless the

catheter is passed through the defect, and the more medial and anterior position of the catheter demonstrated or the catheter passed into one of the vessels of the aortic arch. Retrograde aortography may be valuable if the catheter is positioned in the ascending aorta.

In the 3 patients, aged 15 months, 3 years, and 4 years respectively, subjected to operation under extracorporeal circulation, potassium citrate, hypoxia, or selective cooling was used to produce cardiac arrest. Two patients survived, but one died 12 hours after operation from probable air embolism. The presence of a right-to-left shunt, as in one case in the present series, is considered to be a contraindication to surgery.

R. L. Hurt

533. Congenital Aortopulmonary Septal Defect. Clinical and Hemodynamic Findings, Surgical Technic, and Results of Operative Correction

A. G. MORROW, L. J. GREENFIELD, and E. BRAUNWALD. *Circulation* [Circulation] 25, 463-476, March, 1962. 15 figs., 37 refs.

The diagnostic features of aortopulmonary septal defect and the management of 6 patients suffering from this condition at the National Heart Institute, Bethesda, Maryland, are described. All the patients had a systolic ejection murmur along the left sternal border, and none was found to have a continuous murmur on auscultation or by phonocardiography. Radiologically there were increased pulmonary vascular markings and enlargement of both ventricles. At cardiac catheterization severe right ventricular and pulmonary arterial hypertension was present in every case, with, in 4 cases, an abnormally low femoral arterial diastolic pressure. In 5 cases the left-to-right shunt was large. Indicator dye dilution curves recorded at various sites in the aorta during retrograde aortography in each patient correctly located the level of the shunt.

The septal defect was successfully closed by division and suture in 5 cases. Operation was not carried out in the remaining case because the shunt was right-to-left, and the pulmonary vascular resistance exceeded the systemic resistance. In 2 cases the defect was closed during a period of inflow occlusion under general hypothermia, and in 3 during extracorporeal circulation.

This paper is well illustrated and contains a review of the literature on aortopulmonary septal defect.

R. L. Hurt

534. Interaction of Chronic Hypoxia of Moderate Altitude on Pulmonary Hypertension Complicating Defect of the Atrial Septum

J. E. DALEN, R. A. BRUCE, and L. A. COBB. *New England Journal of Medicine* [New Engl. J. Med.] 266, 272-277, Feb. 8, 1962. 2 figs., 16 refs.

In view of the increased pulmonary arterial pressure produced by the prolonged hypoxia of high altitudes the authors have studied 159 female and 80 male patients with atrial septal defects who had lived for more than 5 years at one of various altitudes ranging from sea level to 5,300 feet (1,615 metres). The diagnosis of atrial septal defect of the secundum type was established by clinical criteria and cardiac catheterization.

Pulmonary hypertension (defined as a mean pulmonary arterial pressure over 35 mm. Hg) occurred as frequently in the group living at low elevations (less than 2,000 ft. (610 m.)) as in those living at moderate elevations (more than 4,000 ft.

(1,220 m.)). Yet only 3 of the 49 patients under 20 years of age living at low elevations had pulmonary hypertension, compared with 11 of 53 of similar age living at moderate elevations. The authors conclude that residence at moderate altitudes, with a consequent chronic exposure to decreased partial pressures of environmental oxygen, contributes to the earlier development of pulmonary hypertension in patients suffering from this type of congenital heart defect.

J. Warwick Buckler

535. The Tetralogy of Fallot: a New Approach to Complete Correction

H. EL SAYED, H. BENTALL, and D. MELROSE. *Lancet* [Lancet] 1, 549-551, March 17, 1962. 1 fig., 8 refs.

Poor results in the surgical correction of the tetralogy of Fallot may be due to inadequate technique. The limiting factor is the size of the pulmonary artery, which must be at least one-third the diameter of the aorta to carry the whole cardiac output. The aim should be complete closure of the ventricular septal defect, and relief of the obstruction to outflow from the right ventricle so that pressure in it falls well below the systemic pressure. This can usually be achieved in acyanotic patients by infundibular resection, and in moderately cyanosed patients by enlarging the outflow tract with a prosthesis. In severely incapacitated patients complete correction is difficult.

The technique now adopted by the authors at Hammer-smith Hospital, London, offers a dry, quiet field without myocardial ischaemia, a disk oxygenator and heat exchanger being used in all cases. Body temperature is lowered with the left ventricle vented until the heart fibrillates, when total by-pass is instituted. The right ventricle is opened and the outflow tract resected, with pulmonary valvotomy if required. The septal defect is repaired by direct suture, if possible, or using a "teflon" felt patch, avoiding heart-block. If necessary a prosthesis of crimped woven teflon to widen the infundibulum is inserted in the ventriculotomy repair.

Postoperative hazards include the low-cardiac-output syndrome (managed by proper blood replacement and correction of acidosis), haemorrhage, and respiratory complications. Of 19 patients operated on with this technique, 2 died; the others are well.

M. Meredith Brown

VALVULAR DISEASE

536. A Critical Review of Aortic Stenosis

R. S. COSBY, B. HEDGE, N. AMSDEN, and M. MAYO. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 203-208, Feb., 1962. 15 refs.

For a review of aortic stenosis 30 patients with this diagnosis were selected from the wards of the Los Angeles (California) County Hospital. All were subjected to a full clinical study, with electrocardiography, radiography, and screening, while left heart catheterization was performed and/or brachial arterial pressure recorded in 24. Ten of the patients who had mitral valvular disease as well as aortic stenosis were studied by combined left and right cardiac catheterization.

Dyspnoea was the presenting complaint in 13 cases and the most frequent symptom in 22. An ejection type of aortic systolic murmur was present in all cases, while the aortic second sound was absent or diminished in 24 cases.

Half the patients had an aortic diastolic murmur, but no evidence of aortic insufficiency. On electrocardiography left ventricular hypertrophy was demonstrated in 26 cases. The majority of pure aortic lesions showed a delayed "onset to peak" measurement in the brachial arterial pressure tracing, but there was no correlation between the contour of the curve and the severity of the stenosis.

All aortic valves catheterized showed a transvalvular gradient greater than 35 mm. Hg. No significant correlation was apparent between the transvalvular gradient and left ventricular pressure and any symptom or sign of aortic stenosis. Therefore it was concluded that the severity of aortic stenosis could not be estimated by clinical or physiological methods.

D. Goldman

537. Mitral Stenosis and Occlusive Thrombosis. (Rétrécissement mitral et thrombus occlusif)

A. BARRILLON and V. BERTRAND. *Archives des maladies du cœur et des vaisseaux* [Arch. Mal. Cœur] 55, 164-171, 5 figs.

The authors report from the Hôpital Boucicaut, Paris, a clinico-pathological observation of occlusive thrombosis of the left auricular-ventricular aperture (ostium venosum) in a woman aged 42 suffering from mitral stenosis. At necropsy the occlusion was found to be due to a massive auricular thrombus measuring 5 cm. in diameter. They point out that the majority of these cases are due to myxoma of the left auricle in hearts free from mitral disease. In this patient the symptoms, which included mental confusion and transitory and repeated collapse, first appeared 7 years before her death and were associated with temporary disappearance of the characteristic auscultatory signs of mitral stenosis.

A. J. Karlish

538. Reoperation for Mitral Stenosis

A. LOGAN, C. P. LOWTHER, and R. W. D. TURNER. *Lancet* [Lancet] 1, 443-449, March 3, 1962. 2 figs., 10 refs.

The authors have reviewed 84 second operations for mitral stenosis, for which in most cases the indication was the recurrence of symptoms after the first operation. In all but 4 restenosis had occurred. It was found that the operative mortality for the second operation had been low and that the results had sometimes been better than on the first occasion. The patients were derived from a series of 264 operated on over 5 years previously (an incidence of 30%); the authors state that symptoms of restenosis seldom appear in less than this time after valvotomy. The incidence of restenosis has risen steeply, 5% of patients requiring a second operation after 5 years, 23% after 8 years, and 60% after 9 years. These figures were, however, taken from the period before the method of transventricular dilatation had been introduced.

When the patients in whom restenosis had occurred and the 184 in whom it had not were compared, little difference between the two groups was found. The reappearance of septal lines was a valuable diagnostic feature, apart from the occasional appearance of right ventricular hypertrophy; the electrocardiogram had not been helpful, but cardiac catheterization did help in the 21 cases in which it was carried out. Active carditis was not responsible for deterioration, but in two-thirds the stenosis was as severe as, or more severe than, it was at the first operation. It was also found that the recorded efficacy of the first operation had no influence on the incidence of restenosis.

The authors suggest that if there is doubt about the diagnosis of restenosis catheterization may be helpful, but that if any doubt remains the valve should be explored. The approach was made through the left side and through a purse-string suture in the left atrial wall. The transventricular dilator was used in all cases.

The incidence and the aetiology of restenosis are discussed. The authors make it clear that the precise mechanism is unknown; but that the incidence certainly rises as the time after the first operation increases. They advise that the second operation should be done early rather than late, particularly if there are signs of pulmonary hypertension, but they are uncertain whether the second operation will halt the inexorable progress of the disease.

J. R. Belcher

DISTURBANCES OF RHYTHM AND CONDUCTION

539. Corticotherapy of Auriculo-ventricular Block. With Reference to 7 Cases. (Corticothérapie des blocs auriculo-ventriculaires. A propos de 7 observations)

J. TORRESANI, M. DELAGE, A. JOBIN, and A. JOUVE. *Archives des maladies du cœur et des vaisseaux* [Arch. Mal. Cœur] 55, 121-130, Feb., 1962. 16 refs.

The successful treatment of auriculo-ventricular block with corticosteroids was first reported in 1954 by Prinzmetal and Kennamer (*J. Amer. med. Ass.*, 154, 1049). Since then other small series of cases have been reported, the total number of patients now exceeding 50. The present paper, from the Centre Cantini, Marseilles, adds 7 cases in which A-V block presenting with the Stokes-Adams syndrome was treated with prednisolone, with successful results in 6 of the 7 cases. In one patient A-V block reappeared each time the dose of prednisolone was reduced below 20 mg. daily; in 4 cases the block persisted, but the cerebral ischaemia was suppressed.

The mechanism of action of the steroids may be due to their anti-inflammatory effect (as suggested by Prinzmetal, whose patient developed the condition during a myocardial infarct), or to their effect on A-V conductivity (in Addison's disease the P-R interval is said to be prolonged). The observation, confirmed by other authors, that steroids may improve the clinical symptoms in spite of the persistence of A-V block cannot be explained, however, by either of the above hypotheses. (In the discussion that followed the paper 3 further cases treated with prednisolone, 30 mg. daily, were reported, of which 2 were successful.)

A. J. Karlish

540. Paroxysmal Ventricular Tachycardia in the Absence of Demonstrable Heart Disease

T. E. HAIR JR., J. T. EAGAN, and E. S. ORGAIN. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 209-214, Feb., 1962. 6 figs., 22 refs.

Three cases of paroxysmal ventricular tachycardia in the absence of demonstrable heart disease are presented. Its occurrence and favourable prognosis in patients without other signs of heart disease are not well appreciated. Diagnosis of this condition becomes certain only after its demonstration by the electrocardiogram. The identification of P waves during the paroxysm, at a slower rate than the ventricular complexes; the presence of a paroxysm of

abnormal ventricular complexes occurring during auricular fibrillation; the onset of tachycardia with an abnormal ventricular complex or a close resemblance, in the same lead, of isolated ectopic QRS complexes to the complexes of the tachycardia are the established criteria for diagnosis. The esophageal lead may be of great help.

Therapy is directed toward removal of precipitating factors and use of procaine amide or quinidine to suppress the ectopic factors. Established bouts require vigorous attention, i.e., parenterally administered procaine amide or quinidine.—[Authors' summary.]

541. Functional Paroxysmal Ventricular Tachycardia

C. W. ADAMS. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 215-222, Feb., 1962. 6 figs., 36 refs.

Paroxysmal ventricular tachycardia can be a functional disturbance. The true incidence of this variety of ventricular tachycardia has not been determined. Nine patients with paroxysmal ventricular tachycardia have been studied at Vanderbilt University Hospital [Nashville, Tennessee], during the past 18 years and no evidence of underlying organic cardiovascular disease was found in these patients. All at present are alive and in good health.

With short paroxysms, symptoms are unimpressive; however, as cardiac output is reduced, syncope, shock or sudden death may occur. The electrocardiogram is the most important single diagnostic procedure; however, it may be difficult to exclude supraventricular tachycardia with bundle branch block or aberrant ventricular conduction. The hemodynamic effects of ventricular tachycardia produce specific clinical manifestations which may suggest the diagnosis.

Although quinidine sulfate and procaine amide are the most effective therapeutic agents in the treatment of all varieties of ventricular tachycardia, the possibility of a serum electrolyte imbalance or a plasma pH alteration must be considered.—[Author's summary.]

CORONARY DISEASE AND MYOCARDIAL INFARCTION

542. Ischaemic Heart-disease: an Assessment of the Value of Reducing Raised Plasma Lipids

M. F. OLIVER. *Lancet* [Lancet] 1, 653-656, March 31, 1962. 18 refs.

It is well known that the plasma cholesterol level is raised in 80 to 90% of males who have ischaemic heart disease before the age of 40. Even in females there is a correlation between a high plasma lipid level and coronary disease, although it is not so marked; this is particularly so after the menopause. It is thus widely assumed that a reduction in the plasma lipid level in those in whom it is raised is desirable. This can be achieved in several ways. A diet in which unsaturated fats, such as corn oil, cotton-seed oil, sunflower oil, or cod-liver oil, are substituted for lard, dripping, and dairy products is a simple and effective way of lowering the blood cholesterol level. Simple reduction of the fat calorie content of the diet to less than 20% of the total caloric intake is effective, but the diet is monotonous and unpalatable. Analogues of thyroxine, which have minimal metabolic effect and lower the blood lipid level, may be useful. Oestrogenic hormones are effective, but

their feminizing action makes them undesirable for use in men. Inhibitors of cholesterol synthesis may lead to accumulation of certain precursors of cholesterol which may be deleterious. Nicotinic acid in large doses is effective, but many patients cannot tolerate the toxic reactions.

Present knowledge of the long-term effects of reducing the serum lipid level in established ischaemic heart disease suggests that this procedure is of little help and that there is still much to be learned about the prevention of this form of heart disease. The author suggests that large-scale trials should be carried out in apparently healthy young men with raised plasma lipid levels. He emphasizes that while interest is focused on this aspect of ischaemic heart disease other factors in the aetiology of the condition, such as smoking, nervous strain, and physical activity, should not be overlooked. G. S. Crockett

543. Long-term Anticoagulant Therapy in Angina Pectoris: a Follow-up Study

C. F. BORCHGREVINK. *Lancet* [Lancet] 1, 449-451, March 3, 1962. 2 figs., 8 refs.

In a study of long-term anticoagulant therapy at Rikshospitalet, Oslo, Norway, 147 patients under 70 who had had angina for less than 2 years but more than 4 weeks were divided into two matched groups. One group (74 patients) received intensive anticoagulant therapy with clotting activity kept at about 20% P.P. (prothrombin-proconvertin); the other group (73 patients) had moderately intensive therapy (P.P. about 50 to 60%). After 2½ years, with an average observation time of 16 months per patient, the moderately treated group were changed to intensive therapy because the results of the latter had been so much better. The final average observation period was 3 years. One patient in the intensively treated group died, whereas 13 died in the other group—a highly significant difference. All deaths were considered to be of cardiac origin, but no necropsy was performed in the cases of sudden death save one. Two other moderately treated patients survived a cardiac infarction. There were 11 cases of bleeding, but only one was serious. The risk at the intensive dosage was computed at one haemorrhage per 17 treatment-years. Some deaths occurred in the previously moderately treated group after the intensive regimen had been substituted.

The author concludes that, for men at least, those who have had angina pectoris for less than 2 years benefit greatly from intensive anticoagulant therapy. He deduces that the intensive regimen is less satisfactory for those with a longer history of untreated angina pectoris, in whom sudden death is not uncommon. J. N. Agate

544. A Clinical Trial of Isocarboxazid ("Marplan") in Angina Pectoris

J. M. BARBER, F. M. MURPHY, and E. A. CHEESEMAN. *British Heart Journal* [Brit. Heart J.] 24, 192-194, March, 1962. 4 refs.

In a double-blind trial isocarboxazid ("marplan"), a monoamine oxidase inhibitor, was compared with lactose as placebo in the treatment of 50 patients with moderate or severe angina. Half the patients were treated first with marplan (30 mg. daily) for 3 weeks and then with placebo for 3 weeks, and the other half in the reverse sequence. Only the pharmacist knew which tablets the patient was taking. Patients were seen weekly by the physicians and

reported success or failure of the treatment on each visit. Nitroglycerin tablets were not discontinued during the trial.

Statistical analysis of the results did not reveal any significant difference between marplan and lactose in the treatment of these patients. Of 25 patients who expressed a preference, 14 favoured marplan and 11 the placebo. When the total series was broken up into groups according to sex, age, and severity of angina the results in these groups showed no exceptions to the general observations. There was a tendency for the patients to prefer the second treatment in both sequences of treatment.

K. G. Lowe

545. Coronary Insufficiency in Man. Physiologic and Electrocardiographic Correlation

R. J. WAGMAN, H. J. LEVINE, J. V. MESSER, W. A. NEILL, N. KRASNOW, and R. GORLIN. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 439-448, March, 1962. 3 figs., 44 refs.

In a study of coronary insufficiency at the Peter Bent Brigham Hospital, Boston, Massachusetts, electrocardiographic findings were correlated with the results of coronary sinus and systemic arterial catheterization in 114 patients. The coronary blood flow was determined by the nitrous oxide technique and the coronary arteriovenous oxygen differences by the method of van Slyke and Neill. In the electrocardiographic studies non-junctional S-T segment depression of 0.5 mm. or more was regarded as abnormal. The report mainly concerns 68 patients on whom the investigations were carried out both at rest and after the Master two-step exercise test. This group was further analysed according to whether they were receiving digitalis or not. In 37 of the patients not given digitalis there was good correlation between the results of electrocardiography during exercise and the characterization of the coronary haemodynamics. Digitalis was found to be a recurrent factor preventing interpretation of the exercise electrocardiogram (ECG). In 26 patients with angina pectoris abnormal haemodynamics were nearly always found, but abnormal exercise ECG patterns were present to a less extent. Out of 9 of these anginal patients who had abnormal ECGs, 8 had abnormalities of coronary flow.

This article further deals in a preliminary fashion with the concept of right-sided angina and right ventricular coronary insufficiency.

P. T. O'Farrell

546. The Relationship between Coronary Blood Flow, Myocardial Oxygen Consumption and Cardiac Work as Influenced by Persantin

V. E. WENDT, J. F. SUNDERMEYER, P. B. DENBAKKER, and R. J. BING. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 449-454, March, 1962. 1 fig., 27 refs.

In a study at Harper Hospital, Detroit, Michigan, coronary blood flow, myocardial oxygen consumption, and cardiac work were estimated both before and after the intravenous administration of 10 mg. of "persantin", a new pyrimidine derivative, in 9 patients not suffering from cardiovascular disease. Methods and procedures are given in detail.

In most of the patients persantin produced a decrease in the coronary vascular resistance. The dissociation between cardiac work and myocardial oxygen consumption suggested that persantin acted on the cellular metabolism, causing an increase in oxygen demands and necessitating an increase

in coronary flow. The administration of persantin resulted in a decline in the ratio of left ventricular work to myocardial oxygen consumption.

It is concluded that this drug, like nitroglycerin, diminishes cardiac work in some patients and has a direct effect on cardiac metabolism.

P. T. O'Farrell

547. Relation of the Degree of Coronary-artery Disease and of Myocardial Infarctions to Cardiac Hypertrophy and Chronic Congestive Heart Failure

L. B. ELLIS, R. B. ALLISON, F. L. RODRIGUEZ, and S. L. ROBBINS. *New England Journal of Medicine* [New Engl. J. Med.] 266, 525-529, March 15, 1962. 1 fig., 14 refs.

The authors report a clinico-pathological study of the coronary vessels of 172 patients with heart disease on whom necropsy had been performed at Boston (Massachusetts) City Hospital. The average age at death was 63 years. All the hearts were injected by a modified Schlesinger technique and multiple sections were studied. Patients with clinical hypertension or nephrosclerosis, as well as those with valvular disease, were excluded.

Cardiac hypertrophy occurred in 17% of those without heart failure who did not have occlusive coronary arterial disease or myocardial infarction, and in about half those with the latter condition. Lesser degrees of coronary arterial disease did not have a clearly demonstrable quantitative influence on the incidence of hypertrophy. In the presence of chronic congestive heart failure, hypertrophy was found in 50 to 60% of patients without occlusions or infarctions and in nearly all those with these lesions. Two alternative methods of grading the degree of coronary arterial disease gave comparable results.

Further investigation of the factors leading to heart failure showed that, of 18 patients in failure with Grade 0 to Grade 2 coronary arterial disease (C.A.D.), all had chronic pulmonary disease, severe anaemia, or myocardial infarctions, with one questionable exception. In 3 of 9 patients with Grade 3 C.A.D. and in one of 14 with occlusive disease none of these circulatory burdens was evident. It was therefore established that chronic heart failure did not occur in this series of ageing persons in the absence of severe C.A.D., infarctions, anaemia, or chronic pulmonary disease.

A. J. Karlisch

548. Treatment of Collapse in Myocardial Infarction. (Лечение коллапса при инфаркте миокарда)

V. N. VINOGRADOV, V. G. POPOV, and A. S. SMETNEV. *Терапевтический Архив* [Ter. Arkh.] 34, 11-19, March, 1962. 7 refs.

The authors report the results of treating 111 patients with myocardial infarction complicated by collapse. Their method consisted in the administration of a slow intravenous drip of noradrenaline in 5% glucose (2 to 6 mg. in 24 hours, according to the severity of the case) combined with 0.25 to 0.5 mg. of strophanthin and 10,000 to 25,000 units of heparin. "Mezaton" (another pressor amine) was given intramuscularly in 1% solution in a dosage of 1 to 2 ml. every 3 or 4 hours, and pain was relieved by administration of a nitrous-oxide-oxygen mixture (1:1) in a closed-circuit apparatus. In the intervals the patient received oxygen in an oxygen tent. As a first-aid measure and during transit to hospital the patient was given mezaton as above and strophanthin intravenously (and in severe cases 0.5 mg. of noradrenaline, by the same route), and gas-oxygen mixture

administered in the ambulance. Opiates were not employed because of their depressing effects upon the respiration and aggravation of the already present anoxia; in addition they tend to lower diuresis. The authors claim a recovery rate of 72%, but only 8 of the 37 patients in Stage III rallied; prompt treatment in the early stages is essential, as with any other method. They state that the intra-arterial injection of blood with the pressor amines should be used only in very severe cases in which intravenous drip has proved ineffective.

L. Firman-Edwards.

549. Treatment of Shock in Myocardial Infarction

A. BERNSTEIN, F. SIMON, E. J. ROTHELD, B. ROBINS, F. B. COHEN, and J. G. KAUFMAN. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 74-81, Jan., 1962. 2 figs., 22 refs.

At Beth Israel Hospital, Newark, New Jersey, 75 patients were treated with mephentermine sulphate in an effort to combat the shock of acute myocardial infarction. This particular drug was selected because it seems to have some physiological and pharmacological advantages over other pressor amines such as noradrenaline and metaraminol. Mephentermine is an inotropic venoconstrictor and not a peripheral arterial constrictor, and thereby increases cardiac efficiency without increasing the likelihood of irreversible shock. It also has some anti-arrhythmic action, which appears to be independent of its vasopressor effect. The drug was given in doses of 60 mg. intravenously or intramuscularly, or both, followed by an intravenous infusion of 600 mg. in 500 ml. of 5% glucose in distilled water; there was no evidence of slough, rash, or other untoward reactions to the drug.

In 57 of the 75 patients, there was an initial adequate rise in blood pressure, and an ultimate survival rate of 41%. Of the remaining 18 patients 13 showed a poor to fair response, but 5 failed to respond at all to mephentermine. In these 5 patients and in those in whom mephentermine failed to maintain its effect noradrenaline was given without, however, any lasting beneficial results. In addition to mephentermine, all patients in the series also received, when necessary, oxygen, digitalis, and morphine to combat the cardiogenic shock.

P. T. O'Farrell

550. Thrombolytic Therapy in Myocardial Infarction

I. H. RICHTER, E. E. CLIFFTON, S. EPSTEIN, F. MUSACCHIO, A. NASSAR, A. G. FAVAZZA, and G. KATABI. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 82-85, Jan., 1962. 8 refs.

In this study reported from Coney Island Hospital, Brooklyn, New York, 116 patients (80 men and 36 women aged 30 to 89 years) with myocardial infarction were given a continuous intravenous drip of thrombolytic for a period of 4 days, immediately on the onset of symptoms or within 20 hours of the acute attack. The technique and dosage are described in detail, together with the results of daily studies of prothrombin time, whole blood clot lysis, euglobulin fibrinolytic activity, and other factors. Of the 116 patients 84 survived and 32 died. A comparative study of the last 52 patients in the series with 52 control patients treated with anticoagulant drugs alone (heparin and warfarin) revealed no significant difference in the mortality rate in these two groups. Side-effects of thrombolytic therapy, in the form of gross bleeding, occurred in 10 of the

116 patients, the greatest incidence of bleeding occurring on the third or fourth day. Although there is some evidence that fibrinolytic therapy provides a direct approach to the dissolution of a clot *in situ* in the coronary artery and to the prevention of myocardial infarction, the authors consider that further studies are required before a firm conclusion as to the value of thrombolytic in the acute phase of myocardial infarction can be drawn.

P. T. O'Farrell

551. Anticoagulants in Acute Myocardial Infarction: a Clinicopathological Study

R. L. RICHARDS. *British Medical Journal* [Brit. med. J.] 1, 820-824, March 24, 1962. 20 refs.

In this paper from the Gardiner Institute, Western Infirmary, Glasgow, the post-mortem findings in 119 fatal cases of myocardial infarction are described. These cases formed part of a series of 446 patients with myocardial infarction, of whom 150 died. The main part of the paper is devoted to a comparison of the findings in patients who had been given anticoagulant drugs with those in patients who for a variety of reasons had not been given this therapy. The two groups were not strictly comparable, but recognizing the limitations of such a comparison the author found that the incidence of the three major thromboembolic complications of myocardial infarction—namely, intracardiac mural thrombus formation, systemic infarction, and pulmonary infarction—was significantly lower among the necropsy subjects who had been treated with anticoagulants than in those not so treated. Despite this finding there was no reduction in mortality in the group given anticoagulant therapy, and the incidence of recent thrombi in the coronary arteries was apparently not altered by such therapy.

Analysis of the data failed to provide any evidence that there was an increased risk of cardiac rupture or of haemopericardium as a consequence of anticoagulant therapy. However, the author mentions particularly 4 patients who developed acute dyspnoea, pleural pain, and haemoptysis who were thought to have suffered pulmonary infarction. At necropsy no evidence of pulmonary infarction was found, but there was a diffuse haemorrhagic lesion throughout the lungs, a probable manifestation of anticoagulant therapy.

A. S. Douglas

HEART FAILURE

552. The Mechanism of Cheyne-Stokes Respiration

R. L. LANGE and H. H. HECHT. *Journal of Clinical Investigation* [J. clin. Invest.] 41, 42-52, Jan. [received March], 1962. 5 figs., 20 refs.

The nature of cyclic respiration and the specific effect of large cyclic variations in blood gas values and pH on the function of the respiratory centre were studied at the University of Utah College of Medicine, Salt Lake City. Simultaneous and continuous measurements of ventilation and of blood gas values were recorded and the lung-to-artery circulation time was estimated in 9 patients with Cheyne-Stokes respiration. Of the 9 patients 8 were males over the age of 59, and all had heart disease; 3 had definite cerebrovascular disease. During the 2-year period of the study 7 of the patients died, necropsy being carried out on 5.

A complete cycle lasted from 48 to 98 seconds. Systemic oxygen saturation was highest at mid-apnoea and lowest at mid-hyperpnoea. The opposite was the case with pul-

monary artery carbon dioxide tension, although no value was above the normal range. As might be expected, alveolar carbon dioxide tension was highest at the close of apnoea and lowest at mid-hyperpnoea. The time of lowest alveolar carbon dioxide tension coincided with the time of highest pulmonary artery carbon dioxide tension. Lung-to-artery circulation time (calculated by subtracting arm-to-lung circulation time from arm-to-artery circulation time) was always prolonged and generally measured about 50% of the respiratory cycle length.

These findings, when compared with analogies in physical systems, support the assumption that the basic mechanism in Cheyne-Stokes respiration lies in the prolonged lung-to-brain circulation time and the loss of effective damping factors. The authors state that the consistent finding of hypocapnia may be partially explained on the basis of congestive heart failure or on the peculiar effects of cyclic variation in oxygen tension on the respiratory centre. Because of the non-linear response this will cause increased mean alveolar ventilation if the amplitude of cyclical variation of pulmonary carbon dioxide tension is such that it falls below the apnoeic point on its downward excursion. Semi-quantitative treatment of the available data yields results which fit the observed depression of the average pulmonary artery carbon dioxide tension without involving "hyper-sensitivity" of the respiratory centre. *G. Clayton*

553. The Retardation of Erythrocyte Sedimentation in Congestive Heart Failure

L. M. SANGHVI and B. M. BOHRA. *British Heart Journal* [Brit. Heart J.] 24, 180-186, March, 1962. 25 refs.

The erythrocyte sedimentation rate (E.S.R.) was determined by the Westergren method at approximately weekly intervals in 35 patients during treatment of congestive heart failure due to coronary, rheumatic, pulmonary, or hypertensive heart disease. At the time of their admission to Sawai Mau Singh Hospital, Jaipur, India, the E.S.R. was increased in 18 patients, and after clinical recovery it was increased in 28 patients. There was no significant change in 5 patients, a decrease in 2, and a significant increase (5 mm. or more) in 28 patients. Change in E.S.R. could not be correlated with any change in total serum protein level, serum albumin and serum globulin fractions, packed cell volume, carbon-dioxide-combining power of plasma, or results of conventional liver function tests. There was, however, a striking correlation between changes in E.S.R. and plasma fibrinogen level, both rising in 23 patients and both falling in 2 patients. It is possible that the retardation of the E.S.R. in heart failure may be due to a decreased blood fibrinogen level resulting from impaired function of the congested liver. *K. G. Lowe*

554. The Relationship of Urinary Potassium Excretion to Dietary Sodium Content in Cardiac Patients Receiving Oral Diuretics

I. S. ESKWITH, J. J. LAWRENCE, and T. MCLOUGHLIN. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 194-202, Feb., 1962. 6 figs., 16 refs.

A study was undertaken at St. Vincent's Hospital, Bridgeport, Connecticut, to discover whether varying the sodium chloride (NaCl) intake of patients taking oral diuretics affected the amount of potassium excreted in the urine. Eleven patients in varying degrees of cardiac failure and

receiving either chlorothiazide or chlorthalidone before and during the study were given a total daily NaCl intake of 15 g. for 5 days and then 0.5 g. for the next 5 days. Results showed that the marked reduction in NaCl intake had little effect on potassium excretion, although it severely restricted sodium excretion. There was no evidence that a high-salt diet interfered with diuresis in this group of patients. Of 4 other patients who had not previously had oral diuretics, 2 were maintained on the high-salt diet for 10 days and 2 on the low-salt diet. They were all given oral diuretics for the last 5 days only, and this led to an increased urinary content of NaCl and potassium, particularly in the patients receiving a low-salt diet.

The results are discussed and explanatory hypotheses presented. *D. Goldman*

PERIPHERAL ARTERIES

555. The Lagging Pulse Sign: an Aid in the Diagnosis of the Cervicobrachial Neurovascular Compression Syndromes

J. D. LAWSON and G. C. SANTOS. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 242, 673-681, Dec., 1961. 1 fig., 26 refs.

The authors describe, from the U.S. Army Hospital, Fort Rucker, Alabama, a new physical sign which they have found useful as an aid in the diagnosis of the cervicobrachial neurovascular compression syndrome and in deciding on the need for surgical treatment. The sign consists in eliciting obliteration of the brachial pulse by such manoeuvres as: (1) getting the patient to turn his head to the side to be examined and holding his breath with the neck extended (Adson manoeuvre), (2) hyperabducting and externally rotating the arm, (3) exerting downward pressure on the backward-projected shoulders, or (4) exercising the arms from the position of rest. On returning the arm to the neutral position it is noted whether or not there is a delay in the return of the radial pulse. A positive sign (the lagging pulse sign) is indicated by a delay of up to 23 seconds and is considered an indication for operative treatment.

Six illustrative cases are reported in some detail, and it is pointed out that in some patients with the syndrome positive signs of muscular or bony pressure on a major vessel or nerve, a sympathetic nerve, or the vasa nervorum may be elicited only intermittently. *H. F. Retchenfeld*

556. The Influence of Some Vegetable Oils on the Blood Levels of Cholesterol and Lecithin in Patients with Atherosclerosis. (Влияние некоторых растительных жиров на уровень холестерина и лецитина в крови больных атеросклерозом)

A. M. PLEŠKOV. *Клиническая Медицина* [Klin. Med. (Mosk.)] 40, 126-130, March, 1962. 6 refs.

This investigation of the effect of vegetable oils on the blood cholesterol and lecithin levels was carried out on 85 patients aged from 40 to 70 years suffering from coronary sclerosis without symptoms of cardiac failure. All the patients were allowed a standard diet, which included 30 to 40 g. of animal fat and supplied 2,800 to 2,900 Calories a day. In addition they received 50 g. of sunflower-seed oil a day, divided into several doses and usually mixed with the food. After 2 weeks the blood cholesterol level fell by a mean of 40 mg. per 100 ml., but when the dose of oil was

increased to 100 g. a day the mean fall was only slightly increased, to 43.4 mg. per 100 ml. The blood cholesterol level quickly returned to the pre-treatment value when the administration of the oil was discontinued. Cotton-seed oil had a considerably less marked effect on the blood cholesterol level.

A. Orley

557. The Therapeutic Value of Vitamin B₁₂ in Atherosclerosis. (Лечебное значение витамина B₁₂ при атеросклерозе)

G. K. LAVSKIJ and D. I. PUŠKINA. *Терапевтический Архив* [Ter. Arkh.] 34, 52-54, March, 1962.

The authors describe their method of treating 58 patients aged from 40 to 80 years suffering from arterial hypertension, cerebral sclerosis, and chronic coronary insufficiency. The majority of the patients had a raised blood cholesterol level and a normal or lowered blood lecithin level. They were treated with vitamin B₁₂ and maintained on a No. 10 Pevsner diet. After treatment the blood cholesterol level fell in 38 of the cases to one-half or less of the previous figure, while the blood lecithin level rose in 41 patients to 2 or 3 times its previous value. There was in many of these patients an imbalance of the blood proteins, the albumin fraction being low and the serum globulin fractions, especially α_1 and α_2 , raised, but following the above treatment the balance in many cases was restored to normal. It is suggested that vitamin B₁₂ tends to correct metabolic disorders, which in the authors' opinion are the basis of atherosclerosis.

L. Firman-Edwards

558. Atherosclerosis: a Comparative Study

R. FINLAYSON, C. SYMONS, and R. N. T-W-FIENNES. *British Medical Journal* [Brit. med. J.] 1, 501-507, Feb. 24, 1962. 7 figs., 17 refs.

The authors have examined the heart, with the aorta and its branches, of 816 animals which died of natural causes at the London Zoological Gardens. Whereas fatty streaking was equally common in mammals and birds (56 out of 233 mammals, or 24%; 119 out of 485 birds, or 25%), only the birds showed a significant number of raised atherosclerotic plaques (87 birds—18%); only 6 mammals (3%) had similar lesions. In the 98 reptiles fatty streaking and atheroma were both rare.

Coronary atheroma was seldom found, and no animal showed atheroma of the coronary circulation alone. The only animal which had anything resembling myocardial infarction was a male Edward's pheasant which had a microscopic focus of myocardial degeneration and necrosis with severe stenosis of a small coronary artery.

In both birds and mammals fatty streaking and atheroma became more common as age increased; the two sexes showed no difference in incidence. Among mammals the aortic lipid-containing lesions were more common in herbivora than in others (carnivora and omnivora); lions, despite their relative inactivity in captivity, were free of lipid lesions. In birds, over-all, atheroma was equally common in herbivora, carnivora, and omnivora, but the Falconiformes, which are meat-eaters, had a very high incidence of atheroma, in contrast to the penguins (fish-eaters), which had virtually no lesions.

The median values for serum cholesterol concentration in birds, mammals, and reptiles were 120, 105, and 75 mg. per 100 ml. respectively, and this was the order of incidence of

atheroma; however, the individual animals with fatty streaking and the birds with atheroma did not show a rise in serum cholesterol level.

Only the birds, therefore (which have a high blood pressure), showed significant atheroma, and it affected the larger arteries and did not show gross ulceration. Thrombotic lesions were almost absent.

The findings do not support the thrombogenic theory of atheroma.

T. B. Begg

559. Effect of Phosphatide Therapy on Blood Lipids

J. B. ENTICKNAP. *British Medical Journal* [Brit. med. J.] 1, 825-827, March 24, 1962. 12 refs.

This communication from East Ham Memorial Hospital, London, records the results of a therapeutic trial of a preparation of phospholipid ("lipostabil") rich in polyunsaturated fatty acids in 114 cases of atherosclerotic disease. The majority of patients received 6 capsules a day, each capsule containing 200 mg. of a selected fraction of soya-bean phospholipids and 1.5 mg. of pyridoxine hydrochloride. The patients were observed for periods up to 2 years, blood tests being carried out initially at fortnightly intervals and then at one month, 3 months, and 6 months.

It was found that whole-blood cholesterol and 9 other fractions of the serum lipids were unaffected by the treatment.

A. I. Suchett-Kaye

HYPERTENSION

560. Clinical Evaluation of Guanethidine Sulfate, a New Antihypertensive Agent

R. G. CHANDRASEKAR, J. O. COPPO, G. W. DUANE, G. PIERRE, M. THURMANN, J. H. UTLEY, and J. G. JANNEY JR. *American Heart Journal* [Amer. Heart J.] 63, 309-319, March, 1962. 2 figs., 22 refs.

The study here reported from St. Louis University Hospital, Missouri, was carried out on 28 patients suffering from essential hypertension of varying degrees of severity, each patient being observed for between 6 months and one year while receiving guanethidine. At the beginning of the study 19 of the patients were being treated for their hypertension with other drugs (most of them with trimethidinium) which were gradually replaced by guanethidine, and for a period many patients were taking two or more drugs. Guanethidine was given initially in a dosage of 12.5 mg. daily before breakfast; the daily dose was increased at weekly intervals by 12.5 mg. until a satisfactory response occurred, or until side-effects (such as orthostatic hypotension) prevented any further increase of dosage. A response was considered as satisfactory when the blood pressure was normal in the standing position. Diet was unrestricted, but sodium intake was limited in patients with congestive heart failure.

The over-all response to guanethidine was excellent, and in general hypertension was better controlled with guanethidine, with fewer side-effects, than with the other drugs tested. With an average daily dose of 73 mg. of guanethidine the blood pressure was lowered to 161/98 mm. Hg in the supine position and 143/89 mm. Hg standing, from mean pre-treatment values of 197/117 and 183/116 mm. Hg respectively. In the early weeks of treatment 10 patients developed diarrhoea, but this abated without alteration in the weekly

increment in dosage. The efficacy of guanethidine was not increased by adding other drugs, such as diuretics, to the regimen, and although this view may need modification when more evidence becomes available, there appeared to be no contraindication to using guanethidine in conjunction with other drugs. No tolerance developed in any patient, and the authors conclude that guanethidine is a very useful and versatile antihypertensive drug.

[In addition to a careful study of the clinical value of guanethidine in the treatment of hypertension, this paper contains a useful review of the pharmacological effects produced by the drug.] W. H. Horner Andrews

561. Guanethidine in Hypertension: Experiences in an East African Hospital

P. P. TURNER. *British Medical Journal* [Brit. med. J.] 1, 914-916, March 31, 1962. 13 refs.

At the Coast Province General Hospital, Mombasa, Kenya, the author has treated 39 severely hypertensive African patients with guanethidine. Of these, 5 died early in the study and only 22 had adequate follow-up—3 to 16 months. A good initial response occurred in 29 patients, but this was not maintained, and of the 22 followed up 2 showed initial resistance and a further 7 developed resistance later. For those in whom the treatment was successfully maintained the dose was high, half of them requiring over 150 mg. daily. The author refers to a further 12 patients of European or Indian stock who all responded to small doses of guanethidine, and suggests there may be a racial or environmental difference to explain the poor results obtained in Africans.

[The observation is an interesting one, but before any conclusions can be drawn it would be important to establish whether the drugs prescribed for out-patients were in fact taken regularly.] C. T. Dollery

562. Serum Uric Acid Levels in Hypertensive Patients Treated with Guanethidine

K. FRY and K. A. BARLOW. *British Medical Journal* [Brit. med. J.] 1, 920-921, March 31, 1962. 1 fig., 12 refs.

The authors report from King's College Hospital, London, a study of the serum uric acid concentration in 22 hypertensive patients before and after treatment with guanethidine. There was no significant change in the serum uric acid level in 20 patients receiving guanethidine alone at the time of the estimation, but of 3 patients who also received chlorothiazide, 2 developed hyperuricaemia. It is suggested that it may be better to reserve the thiazide diuretics for patients proving resistant to guanethidine. C. T. Dollery

563. The Antihypertensive Effects of Chlorthalidone. A Comparative Analysis with Benzothiazide Compounds

J. M. BRYANT, N. SCHWARTZ, S. TOROSDAG, L. FLETCHER JR., H. FERTIG, M. S. SCHWARTZ, R. B. F. QUAN, J. J. McDERMOTT, and T. B. SPENCER. *Circulation* [Circulation] 25, 522-532, March, 1962. 5 figs., 19 refs.

In 83 patients with hypertensive cardiovascular disease control readings of blood pressure were obtained during periods of several months when a placebo only was given. Thereafter chlorthalidone in a maintenance dosage of 200 mg. daily led to falls of 29.3 mm. Hg in mean systolic pressure and 10.2 mm. Hg in mean diastolic pressure. In earlier courses of treatment chlorothiazide, 750 mg. daily, had been

given to 50 of the patients and hydrochlorothiazide, 75 mg. daily, to 48 of them. The hypotensive response to chlorthalidone was significantly greater than that to chlorothiazide, and greater, but not significantly so, than was the case with hydrochlorothiazide. The addition of reserpine, 0.1 to 0.5 mg. daily, to chlorthalidone led to a further significant fall in blood pressure. No tolerance to chlorthalidone was observed, and its hypotensive effect was not influenced by age, sex, or known duration of hypertension. While a significant fall in blood pressure occurred in the mild as well as the moderate and severe cases of hypertension, the hypotensive effect was greater in the patients with the more severe hypertension. Side-effects were rather less severe with chlorthalidone than with the other drugs. K. G. Lowe

564. Aldosterone Secretion in Hypertensive Diseases

C. L. COPE, M. HARWOOD, and J. PEARSON. *British Medical Journal* [Brit. med. J.] 1, 659-665, March 10, 1962. 4 figs., 21 refs.

The possible role of aldosterone in the production of hypertension was studied in 22 hypertensive subjects at the Postgraduate Medical School (Hammersmith Hospital), London. The aldosterone secretion rate was measured by injecting a small amount of tritium-labelled aldosterone intravenously; this is metabolized in the normal way in the body and is subsequently excreted, mainly in the urine. Since all the urinary aldosterone metabolites, unknown or otherwise, will then contain the same proportion of labelled compound, it becomes possible to measure the total quantity by determining the specific activity of any one metabolite and then measuring the total isotope content in the urine. Preliminary measurements showed that only about 65% of aldosterone metabolites were excreted in the urine, a further 25% probably being eliminated in the stools via the bile. In addition, a more accurate assessment of aldosterone excretion rate in diseased kidneys was obtained by using a modified formula, since renal impairment is a frequent finding in severely hypertensive subjects.

Aldosterone secretion rates were then assessed in 22 patients with severe hypertension of varied aetiology, and compared with those in 22 normotensive but ill patients with various metabolic disturbances. The mean secretion for the hypertensives was 227 μ g. daily, with a wide scatter of individual results, and for the normotensives 209 μ g. daily, again with a wide scatter, and no significant difference was evident. More detailed analysis showed a greater range of values in hypertensive subjects, and the aldosterone secretion rate may be very high in malignant hypertension, but not invariably so. Abnormalities in the pyelogram or the presence of stenosis of the renal artery did not significantly affect the results.

The literature relating aldosterone production and hypertension is reviewed and the possible factors responsible for modifying aldosterone secretion in hypertension are considered. Angiotensin, although a potent stimulator of aldosterone secretion, is not considered of any aetiological significance in essential hypertension. In some patients with malignant hypertension it is suggested that sodium retention may be a factor in reducing aldosterone excretion.

The authors conclude that uncomplicated hypertension does not raise the aldosterone excretion rate, and there is no evidence to suggest that aldosterone plays any part in its pathogenesis. Gerald Sandler

Clinical Haematology

565. Hereditary Benign Erythroreticulosis

I. BERGSTROM and L. JACOBSSON. *Blood [Blood]* 19, 296-303, March, 1962. 3 figs., 18 refs.

Benign erythroreticulosis, which appears to be a rare condition, was observed in 15 members of a family living in the province of Västerbotten, North Sweden. The disease affects both sexes, but the pattern of inheritance is not clear. There is a moderate normochromic anaemia refractory to all haematopoietic agents [but steroids were not tried]. There are marked anisocytosis and some macrocytosis; a few cells contain nuclear remnants. Erythropoiesis alone appears to be affected; it is hyperplastic and characterized by the presence of multinucleated "gigantoblasts" resembling those sometimes seen in the Di Guglielmo syndrome. The erythrocytes contain an abnormal haemoglobin which behaves electrophoretically like foetal haemoglobin but in other respects resembles adult haemoglobin. The condition is benign and some affected persons are over 70 years of age. Erythrocyte survival is normal and there is no hepatomegaly, splenomegaly, or lymphadenopathy.

R. B. Thompson

566. Acquired Hemolytic Anemia and Associated Thrombocytopenic Purpura with Special Reference to Evans' Syndrome

M. N. SILVERSTEIN and F. J. HECK. *Proceedings of the Staff Meetings of the Mayo Clinic [Proc. Mayo Clin.]* 37, 122-128, Feb. 28, 1962. 8 refs.

The authors reviewed 399 cases of haemolytic anaemia and 367 of thrombocytopenic purpura seen at the Mayo Clinic between 1950 and 1958. In 6 of these 766 cases the criteria for the diagnosis of Evans's syndrome were fulfilled—namely, (1) acquired haemolytic anaemia and thrombocytopenic purpura affecting a single patient, the abnormalities occurring together or in succession; (2) absence of any apparent secondary aetiological factor; and (3) a positive response to Coombs's test at some time during the illness. Of the 6 patients, 4 died. Splenectomy resulted in prolonged benefit in only one patient.

In 19 further cases acquired haemolytic anaemia and thrombocytopenic purpura were associated with an underlying disease—cirrhosis (5), chronic nephritis (2), thrombotic thrombocytopenic purpura (2), tuberculosis (1), lupus erythematosus (1), and lymphoma or leukaemia (8).

The authors regard Evans's syndrome as an autoimmune disease in which erythrocytes and platelets are the prime targets. They emphasize that remissions and exacerbations of haemolytic anaemia and thrombocytopenic purpura are the outstanding clinical features and that prognosis should be guarded.

J. V. Dacie

567. Pyruvate Kinase (PK) Deficiency Hereditary Non-spherocytic Hemolytic Anemia

K. R. TANAKA, W. N. VALENTINE, and S. MIWA. *Blood [Blood]* 19, 267-295, March, 1962. 5 figs., 40 refs.

The authors of this paper from the University of California Medical Center and Wadsworth Hospital, Veterans Administration Center, Los Angeles, describe 7 cases con-

forming to Type-II congenital non-spherocytic haemolytic anaemia. Type II is differentiated from Type I by, among other features, the markedly increased autohaemolysis on incubation of sterile defibrinated blood not correctable by the addition of glucose. In these cases there is great variability in the severity of the haemolytic process; icterus is inconstant, and slight to moderate splenomegaly is usual. Splenectomy is only occasionally of appreciable benefit. Erythrocytes are normochromic, there is no spherocytosis, and only slight anisocytosis and poikilocytosis are seen. There is a fairly uniform moderate macrocytosis consistent with the reticulocytosis. Many features described in earlier cases, such as Pappenheimer bodies, appear to be the result of splenectomy.

In the present series of cases the authors repeatedly demonstrated in the erythrocytes, but not the leucocytes, a deficiency of pyruvate kinase. In one case the deficiency was corrected by the addition of the crystalline enzyme; no inhibitory substance was detected. The defect is probably transmitted as an autosomal recessive; heterozygotes have a partial enzyme deficiency but no clinical disease.

A full account is given of the methods used and of the very detailed observations made.

R. B. Thompson

568. The "Escape" Phenomenon of Polycythemia Vera: Its Relation to Hemorrhage and Thrombosis in the Disease

T. W. SHEEHY and G. MONTALVO. *American Journal of the Medical Sciences [Amer. J. med. Sci.]* 243, 183-192, Feb., 1962. 4 figs., 25 refs.

It has been demonstrated that when blood from a patient with polycythaemia vera is allowed to clot in a test-tube a small clot forms which is surrounded by serum containing a deep layer of sedimented erythrocytes. This "escape" phenomenon has been attributed to high platelet counts. It has been suggested that clot retraction takes place so rapidly that erythrocytes are forced out of the clot. The object of the study here reported from the U.S. Tropical Research Laboratory, San Juan, Puerto Rico, was to investigate the coagulation mechanism in a group of 6 patients with untreated polycythaemia vera, and to determine whether the escape phenomenon was related to haemorrhage in this disease.

Coagulation studies performed on the 6 patients gave results within normal limits, though the escape phenomenon was evident in each case in the polycythaemic clots, which were smaller than those obtained from 10 normal control subjects, and the volume of erythrocytes escaping into the serum always exceeded that observed in the control clots. When oxalated plasma was clotted by the addition of thrombin, the resulting clot volume depended to some extent on the platelet concentration. Platelet-deficient plasma yielded large clots, whereas plasma with platelet concentrations exceeding 100,000 per c.mm. produced small clots of almost constant volume. The thromboelastograms of whole blood with elevated erythrocyte and platelet concentrations were abnormal and resembled those observed with whole blood from polycythaemic patients with haemorrhage.

A disorganization of the fibrin network has been found in polycythaemia. Instead of being uniformly distributed and regular in appearance, the fibrin strands are irregular and punctured with numerous holes. This would allow for an increased number of cells to "escape" into the serum. The erythrocyte mass in polycythaemia increases without a proportionate rise in the plasma volume, thus reducing the concentration of fibrinogen by 10 to 30%. This probably contributes to the irregular fibrin mesh. It is suggested that the triad of excess abnormal platelets, an increased erythrocyte mass, and the relative fibrinogenopenia in polycythaemia probably all interfere with adequate clot formation and thereby contribute to the bleeding.

A. W. H. Foxell

HAEMORRHAGIC DISEASES

569. Evaluation of Corticosteroids in Hemophilia: a Controlled Study during Oral Surgery

N. TRIEGER and J. J. MCGOVERN. *New England Journal of Medicine* [*New Engl. J. Med.*] **266**, 432-437, March 1, 1962. 3 figs., 27 refs.

A controlled study of the value of prednisone as an adjunct to plasma replacement therapy in 5 patients with haemophilia and 3 with Christmas disease undergoing tooth extraction is described in this paper from Massachusetts General Hospital, Boston. A group of 8 patients were subjected to dental extractions on two separate occasions; on one occasion they received infusions of plasma and on the other plasma infusions together with prednisone. On the basis of the number of days on which bleeding occurred, the duration of stay in hospital, plasma infusion requirements, and the amount of replacement blood given, it was considered that prednisone had a significantly beneficial effect. The use of dental splints during extraction was found to be unnecessary. No untoward side-effects were observed.

A. S. Douglas

570. Evaluation of Platelet Antibodies in Idiopathic Thrombocytopenic Purpura

M. CORN and J. D. UPSHAW JR. *Archives of Internal Medicine* [*Arch. intern. Med.*] **109**, 157-167, Feb., 1962. 42 refs.

In an attempt to demonstrate the presence of antibodies to platelets in idiopathic thrombocytopenia (I.T.P.), the authors, working at Johns Hopkins University and Hospital, Baltimore, employed a number of methods, including fluorescent techniques and agar gel diffusion. In addition, they used a platelet agglutination test and studied the effect of I.T.P. serum on clot retraction, and the ability of I.T.P. serum and serum containing a platelet isoantibody to block agglutination activity of rabbit antihuman platelet (A.H.P.) serum. Studies *in vivo* included the ability of human plasma and rabbit plasma to cause thrombocytopenia in dogs and passive cutaneous anaphylaxis in the guinea-pig.

The result of fluorescein conjugation was the failure of all 16 specimens of sera from patients with I.T.P. to produce fluorescence on platelets fixed on marrow smears. However, conjugated rabbit antihuman platelet serum produced fluorescence under the same conditions to a titre of 1:128. Neither antibodies to platelets nor megakaryocytes were demonstrated, thus confirming the findings of previous workers. In the agglutination tests there was no significant difference between the control sera and the sera from 19 patients with I.T.P.; both produced agglutination of

platelets to an equal extent. The effect of the I.T.P. sera on clot retraction did not differ from that of control sera, nor did the incubation of normal platelets in I.T.P. serum prevent the agglutination of the platelets by rabbit A.H.P. serum. It was concluded that antibodies were not producing a blocking effect. No reaction was obtained when serum from 11 patients with I.T.P. was tested by agar gel diffusion against platelet suspension.

Depression of the platelet count in dogs by as much as 75 ml. of I.T.P. serum was transitory. On the other hand, 5 ml. of rabbit A.H.P. serum caused virtual disappearance of circulating platelets for days. Serum from 15 patients with I.T.P. was injected into guinea-pigs, and 4 hours later a mixture of platelets and azovan blue was given intravenously. None of the 15 specimens of test serum or of 7 control specimens produced a positive reaction, indicated by a blue-stained area at the site of injection when the animals were killed 45 minutes later.

The authors conclude that none of the methods gave any indication of a platelet antibody in I.T.P. After reviewing the literature, they suggest that their work does not exclude the possibility of an antibody in low concentration. I.T.P. could also be due to an antibody which may differ from the classic antibodies to such an extent that present methods of detection are unsuitable.

J. S. Malpas

571. Haemorrhagic Diathesis in Liver Disease with Special Reference to Thrombocyte Function. (Hämorrhagische Diathesen bei Lebererkrankungen unter besonderer Berücksichtigung der Thrombocytenfunktion)

K. BREDDIN. *Acta haematologica* [*Acta haemat. (Basel)*] **27**, 1-16, 1962. 4 figs., 35 refs.

Disturbance of thrombocyte function in liver disease has been relatively rarely described. It may occur in the presence of a normal platelet level, but failure of clot retraction and enzyme disturbances which indicate injury of the liver parenchyma have been observed and may be associated with hypoprothrombinaemia, increase of fibrinogen, and alteration of consistency of the thrombus. From the University Medical Clinic, Frankfurt-on-Main, the author describes a case of chronic hepatitis with a haemorrhagic diathesis in which the clinical picture was that of thrombocytopenia but the level of thrombocytes was normal. In such cases functional disturbance has been present in the form of defective clot retraction and of diminished adhesive capacity and resistance of the thrombocytes, and as shown by the thromboelastogram.

An investigation of the thrombocyte function in 130 patients with hepatic cirrhosis, chronic hepatitis, biliary cirrhosis, obstructive jaundice, and acute hepatitis was therefore carried out by various methods, including thromboelastography and blood coagulation and platelet function tests. Deficient clot resistance was present in two-thirds of the patients with cirrhosis and chronic hepatitis, in 3 this being combined with thrombocytopenia, in one with fibrinogen deficiency, and in the remainder with various disturbances of thrombocyte function. This deficiency was absent in all but 2 of the cases of acute hepatitis, while clot resistance was normal or increased in biliary cirrhosis and obstructive jaundice. Retraction of the plasma clot was diminished in all the cases with decreased resistance of the blood thrombus. Marked purpura was present in 3 cirrhotic cases, a few petechiae were seen or a positive

Rumpel-Leeds test result in 5, while in 3 others, with a thrombocyte count of less than 100,000 per c.mm., there were petechiae and bleeding from mucous membranes. In 81 patients with cirrhosis and 23 with chronic hepatitis the blood platelet count was normal.

Delayed coagulation time was present in 3 cases, but Factor III was normal in the few cases examined. Delayed thromboplastin time was a frequent finding; decrease of Factor VII was especially marked in decompensated cirrhosis, and of Factor V more frequently than in chronic hepatitis; delayed thrombin formation was of equal frequency in both types of disease. Slight fibrinogenopenia was present in only 3 cases; in obstructive jaundice and biliary cirrhosis the fibrinogen level was above 400 mg. per 100 ml. Prothrombin consumption was abnormally high in 3 cases showing thrombocytopenia and in some cases of cirrhosis and chronic hepatitis. Thrombokinas factors (Factor VIII and serum factors) were estimated only in patients with purpura and without thrombocytopenia; these factors were not diminished.

No relationship was established between thrombocyte function disturbance and clinical severity of the disease or pathological liver function test results. Nor was any relation between splenic hyperaemia and thrombocyte function apparent in this investigation, but a case is cited in which a high degree of disturbance of thrombocyte function and a haemorrhagic diathesis, with a normal platelet count, and not associated with abnormality of liver function, were restored to normal by splenectomy. The author suggests that splenectomy should be considered in cases of cirrhosis or chronic hepatitis where a severe haemorrhagic diathesis is associated with thrombopathy. He points out that some reported cases of defective thrombocyte function bear a marked resemblance to hereditary thromboasthenia; he does not agree that the petechial lesions in liver disease are due to toxic injury of the capillaries.

Ethel Browning

NEOPLASTIC DISEASES

572. **Lymphography in Hodgkin's Disease (a Study of 45 Cases).** (La lymphographie dans la maladie de Hodgkin (étude de 45 cas))

G. MARCHAL, J. BERNARD, N. ARVAY, G. BILSKI-PASQUIER, J. D. PICARD, G. MATHÉ, and G. BRULÉ. *Nouvelle revue française d'hématologie [Nouv. Rev. franç. Hémat.]* 2, 4-26, Jan.-Feb. [received April], 1962. 13 figs., 9 refs.

This paper from the Hôpital Broussais and Hôpital Hérold, Paris, describes the use of a new technique of lymphography in which a fat-soluble radio-opaque substance is injected into the dorsum of the leg, the lymphatics of which have been previously outlined by means of a coloured dye. After the injection, which can be given with a needle or a fine catheter, radiographs are taken at intervals from 30 minutes to 4 hours afterwards. Only one untoward incident, the development of lymphangitis, was observed in a series of 150 examinations by this technique.

The abnormalities found in the 45 cases investigated are described and illustrative cases discussed. In one interesting case of Hodgkin's disease of the retroperitoneal lymph nodes these were clearly outlined by means of lymphography and a simultaneous intravenous pyelogram showed that the ureter was involved in the mass of nodes. The

authors suggest that the finding of 23 patients with unsuspected enlarged nodes out of 45 cases of Hodgkin's disease justifies the further use of this method whenever lymph-node enlargement is suspected.

I. McLean Baird

573. **Malignant Lymphomas: Classification, Prognosis, and Treatment**

G. HILTON and P. M. SUTTON. *Lancet [Lancet]* 1, 283-287, Feb. 10, 1962. 15 refs.

The authors set out to determine whether the pathology of a lymphomatous condition should influence the method of treatment and to assess the value in prognosis of the classification of lymphomata of Gall and Mallory. An attempt was also made to correlate clinical staging in cases of lymphoma, as suggested by Craver and Peters, with prognosis.

Biopsy material and the history in all cases in which lymphoma had been diagnosed at University College Hospital, London, since 1946 were re-examined and 363 cases were considered definitely to be lymphomatous as follows: Hodgkin's lymphoma in 152 (classic in 137, paraganuloma in 12, sarcoma in 3); giant follicular lymphoma 39 (well-differentiated in 32 and poorly differentiated in 7); reticulum-cell sarcoma 85 (stem-cell in 10, clasmaticocytic in 75); and lymphosarcoma 87 (lymphocytic in 47 and lymphoblastic in 40). Of these, 275 were first diagnosed more than 5 years previously and form the basis of the survival figures.

The results of surgery were less favourable than those of radiotherapy or chemotherapy. Moderate doses of x rays spread over several weeks were preferred to radical doses and gave as good results without immediate or late post-irradiation changes. With multiple node involvement, except in cases of Hodgkin's disease with toxæmic symptoms, irradiation gave better results than chemotherapy. With the exception of cases of well-differentiated giant follicular lymphomata, which responded to lower doses of x rays, histology was of no help in deciding the level of dosage, the same dose having the same effect provided the physical state of the lesions was comparable. It is pointed out that useful remissions have recently been obtained [since 1956] with corticosteroids in a few cases of lymphosarcoma and Hodgkin's disease.

The 5-year survival rate in the group of patients with Hodgkin's disease was 31%, but a striking finding was the 5-year survival of 6 out of 8 patients with paraganuloma, indicating the value of separating this histological type with its much better prognosis from classic Hodgkin's disease. Hodgkin's sarcoma was diagnosed in only 3 cases, and the authors consider that such cases are better classified as reticulum-celled sarcoma. Clinical staging was helpful in prognosis only in Hodgkin's disease, the 5-year survival rate being 79% in Stage I compared with 3% in Stage III. In the cases of well-differentiated giant follicular lymphoma the 5-year survival rate was 50%, in those of reticulum-celled sarcoma it was 16% (there being no advantage in subdividing these into stem-celled and clasmaticocytic), and in cases of lymphosarcoma it was 29%; patients with the lymphocytic type doing only a little better than those with the lymphoblastic type.

The authors suggest that only five main types of lymphomata need be recognized: reticulum-celled sarcoma, lymphosarcoma, giant follicular lymphoma, Hodgkin's disease, and Hodgkin's paraganuloma.

A. Ackroyd

Respiratory System

574. **Cystic Fibrosis in Adults. Studies of Pulmonary Function and Some Physical Properties of Bronchial Mucus.** G. POLGAR and R. DENTON. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 319-327, March, 1962. 5 figs., 20 refs.

Cystic fibrosis is a disease of the exocrine system of unknown aetiology which affects mainly the gastro-intestinal and respiratory tracts. When the respiratory system is predominantly involved, the disease may run a protracted course ending in respiratory insufficiency. Only 2% of patients with the disease survive the age of 20 years. The authors, in this paper from the Pennsylvania University School of Medicine, Philadelphia, report the results of respiratory function studies in 4 patients over the age of 20 (3 male and one female), 2 of whom came to necropsy. Sputum viscosity studies showed that mucus of patients with cystic fibrosis possessed a resistance to initial flow more than 100 times that of control mucus. All 4 patients had severe disturbance of respiratory function. Total lung capacities were not markedly increased, but residual volumes were at levels even higher than those found in severe obstructive emphysema. A consistent unevenness of distribution of inspired air, a decrease in maximal expiratory flow rates, and an increase in airway resistance all pointed to an obstruction of the lower airways. The lungs were stiff, as indicated by low compliance values; this, the authors believe, was due largely to obstruction of some lung units, since there was no evidence of diffuse fibrosis in the results of lung function tests or in the morbid histology. Airway obstruction did not respond to bronchodilator drugs.

It is concluded that abnormal bronchial mucus is the primary cause of the lung disease. The retained mucus narrows the airways, increases resistance to the flow of air, and occludes some bronchi completely, causing atelectasis. Stagnation of mucus provides a favourable nidus for endobronchial infection, which results in mucosal oedema and further narrowing of the airways. T. Semple

575. **Chronic Bronchitis: a Five-year Follow-up** V. C. MEDVEI and N. C. OSWALD. *Thorax* [Thorax] 17, 1-4, March, 1962. 1 fig., 2 refs.

* At the Brompton Hospital, London, between 1952 and 1953 a series of 312 civil servants (286 male and 26 female) with a history of recurrent sickness absence for bronchitis were subjected to full clinical and radiological examination. Five years later they were recalled for a second examination; of the 312 patients 96 had died and only 7 were untraced. The mortality was excessive at all ages. The ratio of observed to expected deaths was 4.2 in the males and 3.3 in the females. Respiratory diseases were the cause of death in 57 cases, but there was also an excessive number of deaths from cardiovascular diseases. The ratio of observed to expected deaths was greater in the younger men and declined with increasing age. In the younger, more disabled, bronchitics the prognosis was extremely poor, the 5-year death rate being 38% in patients under 50. On the other hand, the absolute death rate was higher and the lia-

bility to clinical deterioration was greater in the older patients. It is considered that the figures in this paper provide a basis on which the prognosis in patients with bronchitis of various degrees of severity may be assessed.

C. M. Fletcher

576. **Chronic Bronchitis: Radiological Aspects of a Five-year Follow-up**

G. SIMON and V. C. MEDVEI. *Thorax* [Thorax] 17, 5-8, March, 1962. 1 fig., 4 refs.

The authors discuss the radiological features in 299 of the 312 patients with chronic bronchitis described in Abstract 575. The radiological criteria used for the diagnosis of emphysema included a low, flat diaphragm, an increase in the retrosternal translucent area, decrease in diaphragmatic movement, a narrow vertical heart, and large hilar vessels with decrease in the size of the peripheral intrapulmonary vessels. Localized avascular areas of over-distension, indicating bullae, were recorded as localized emphysema.

The proportion of patients with evidence of emphysema increased with age. The 5-year mortality rate was twice as high in patients with emphysema as in those with normal chest radiographs or with only localized emphysema. The mortality rate was highest in patients with evidence of generalized emphysema between the ages of 40 and 59. The degree of dyspnoea was also higher in those with radiological evidence of generalized emphysema than in patients with a normal chest radiograph. There was very little change in the radiological appearances in the course of the 5-year follow-up. C. M. Fletcher

577. **The Tumour-like Forms of Aspergillosis of the Lung (Pulmonary Aspergilloma). A Report of Five New Cases and a Review of the Portuguese Literature**

T. G. VILLAR, J. CORTEZ PIMENTEL, and M. FREITAS E COSTA. *Thorax* [Thorax] 17, 22-38, March, 1962. 16 figs., 25 refs.

Five new cases of pulmonary aspergilloma are presented and the 30 cases reported up to now in Portugal are reviewed. All these patients had disease in their lungs before the aspergillus invaded them (bronchiectasis, lung abscess, bronchogenic cyst, echinococcus cyst, and tuberculosis). In some cases the invasion of cavities by the parasite could be followed radiographically.

Aspergilloma is found more frequently in the lower lobes than is generally thought: since lesions in this location are more likely to be infected, it appears in one of its "residual forms". The fungus once in the lung grows and dies continuously, and as it dies the mycelium calcifies. Only in 4 of the cases discussed was the fungus mostly "alive". In 9 it was completely "dead" and in 4 of these calcified (2 wholly calcified). A morphological criterion for "dead" and "alive" fungus, which correlates closely with the results of cultures, is presented and a pathogenic theory is developed in which the fungus is followed from "initial stages" to "residual stages" ending in necrosis and elimination or calcification. Haemoptysis and blood streaking dominated

the clinical picture of the great majority of patients, the syndrome of pulmonary suppuration coming next.

Besides the classical "bell-like" image other radiological aspects are described, such as sausage-like intracavitary masses, masses containing air bubbles, stratification of the intracavitary masses, partial calcification, and coral-like calcification. In 4 cases in which the cavity was penetrated by the contrast during bronchography the fungus mass was displaced by the contrast, which was another proof of the mobility of the fungus ball within the cavity.

Lobar resection is considered the treatment of choice.—
[Authors' summary.]

NEOPLASTIC DISEASES

578. Heavy Smokers with Low Mortality: a 14½-Year Test of the Cigarette Hypothesis of Lung Cancer Causation

J. COHEN and R. K. HEIMANN. *Industrial Medicine and Surgery* [Indust. Med. Surg.] 31, 115–120, March, 1962. 13 refs.

The mortality among employees in the cigarette division of a large American tobacco company during the period 1946–56 has been previously reported by Dorn and Baum (*Indust. Med. Surg.*, 1955, 24, 239) and by Haag and Hammer (*Indust. Med. Surg.*, 1957, 26, 559). In the present report data are added for a further period of 4 years (1957–60) and the observed mortality among the full-time and retired employees over the 14½ years from October, 1946, to December, 1960, is compared with the expected mortality calculated from the death rates by age, sex, and colour for the whole population of the U.S.A.

In the past 4 years the number of deaths from all causes (325) among the employees was found to be only 76% of the expected number (425). For all forms of cancer the observed number was 63% of the expected (47 against 75); for cancer of the respiratory system it was 43% of the expected (6 against 14), and for coronary arterial disease it was 86% of the expected (100 against 116). For the whole period of 14½ years the proportions were: all causes 71%, all cancers 70%, cancer of the respiratory system 71%, and coronary disease 79%. It has been previously shown that employees of cigarette-making companies contain a higher proportion of regular cigarette smokers and also of persons smoking more than 20 cigarettes a day than the general population of the U.S.A., and it is concluded that the data now reported tend to disprove the hypothesis that smoking causes a higher mortality from all causes or from any of the particular causes which have been specially studied. *Richard Doll*

579. Bronchial Adenoma

S. ZELLOS. *Thorax* [Thorax] 17, 61–68, March, 1962. 6 figs., 31 refs.

Over a recent 12-year period 40 patients (23 female and 17 male) with bronchial adenoma were seen at the Regional Thoracic Unit in Edinburgh. During the same period at this unit 3,000 patients with bronchial carcinoma were studied.

Histologically, 33 of the tumours were of the carcinoid type, 6 were cylindroid type, and one showed features of both types. Hilar lymph-node metastases were found in 10 of the patients with the carcinoid type and in 2 with cylindromata. Hepatic metastases developed in 2 patients with

carcinoid tumours, and in one of these manifestations of the carcinoid syndrome were subsequently seen.

Resection was carried out in 38 patients. In view of the potential malignant nature of the tumours the author considers that the minimum safe resection is a lobectomy, but often more extensive resections are necessitated by lung damage. The lesion is eminently suitable for "sleeve resection" in selected cases. The hilar lymph nodes should be removed in addition. Endoscopic removal is considered unwise and the tumours are relatively insensitive to irradiation.

Of the 38 patients operated on 30 were alive at the time this paper was written. There was one operative death from pulmonary embolism, and of the 7 late deaths 5 were associated with recurrence either locally (one patient with tracheal cylindroma) or at a distance. Ten of the patients with hilar lymph-node involvement were still alive.

The author considers that bronchial adenoma is a malignant tumour which invades and metastasizes to both lymphatic nodes and distant organs. *W. P. Cleland*

580. Sex Differences in the Survival of Lung Cancer Patients

F. EDERER and W. L. MERSHEIMER. *Cancer* [Cancer (Philad.)] 15, 425–432, March–April, 1962. 2 figs., 27 refs.

This report is based on 7,547 white male and 1,260 white female patients with microscopically confirmed carcinoma of the lung diagnosed between 1950 and 1957; the cases were collected by 3 central and 7 individual cancer registries taking part in the "End-Results Evaluation Program" sponsored by the U.S. National Cancer Institute, Bethesda, Maryland. The difference in relative 5-year survival rates in patients with localized disease (forming only 17% of the total) was striking, namely, 20% in males and 41% in females. The difference for those with regional spread was small and there appeared to be no significant difference between male and female patients with metastases. Only patients treated by surgery appear to have much chance of survival, and for male patients with localized disease the 5-year relative rates for the following forms of treatment were: surgery 35%, radiotherapy 2%, surgery plus radiotherapy 14%, chemotherapy and/or hormonal therapy nil, and other treatment or no treatment 2%. Relative cumulative 5-year survival rates for surgically treated patients with localized disease were 35% for men and 68% for women, a difference significant to the 0.001 level. In fact, for women with localized disease the curve levelled off at 2½ years, 99% surviving the further 2½ years. Analysis of possible factors causing this difference, such as operative mortality, histological type of the tumour, and age differences (31% of the men, but only 15% of the women, with localized disease were 65 years of age and older), and several other factors, did not reveal that any one of these was responsible.

The authors note that British data on survival of women are in approximate agreement with the present figures for the U.S.A. They also point out that in 16 out of 20 other forms of cancer the 5-year survival rate is greater for women than for men. The effect of smoking is also briefly discussed. It is suggested that in lung carcinoma a sex-associated factor may inhibit tumour spread, although so far hormonal treatment has been unsuccessful. Further research on clinical, epidemiological, immunological, and therapeutic lines is recommended. *B. Golberg*

Urogenital System

581. Long-term Treatment of Pyelonephritis and other Urinary Tract Infections with a New Combination of Sulfanilamides

P. A. ÖRSTEN, H. BUCHT, Å. HOLMGÅRD, and B. JOSEPHSON. *Journal of Urology* [J. Urol. (Baltimore)] 87, 220-229, March, 1962. 24 refs.

From St. Erik's Hospital, Stockholm, the authors report the results obtained with a combined tablet of long-acting and short-acting sulphonamides in the treatment of 68 patients with chronic urinary tract infections. The tablet has a core of 0.25 g. of sulphamethyldiazole and an outer layer composed of 0.15 g. of sulphamethyldiazole and 0.10 g. of sulphamethoxyypyridazine; the outer layer dissolves in the gastric juice and the inner core, which is resin-treated, dissolves slowly in the gut. Twice-daily dosage was adjusted so as to obtain an adequate serum sulphonamide level of 8 to 12 mg. per 100 ml. and good renal excretion of 50 to 130 mg. per hour. Most of the patients had infections due to *Escherichia coli* accompanied by frequent anatomical complications.

In 62 of the 65 patients the urine became sterile, though in many cases antibiotics and nitrofurantoin had to be given in addition. There were 12 relapses during treatment, the duration of which varied from a few months to years, and there were 10 relapses after stopping the treatment, though stopping was often against medical advice. The authors consider that this form of treatment shows promise in chronic urinary infections.

Arnold Pines

582. Aminoaciduria in the Course of the Nephrotic Syndrome in Children. The Influence of Hormonal Therapy. [In English].

C. HOOFT and J. HERPOL. *Annales paediatrici* [Ann. paediat. (Basel)] 198, 3-23, 1962. 25 refs.

The authors of this paper from the Paediatric Clinic of the State University, Ghent, Belgium, describe the pattern of amino-acid excretion, as determined by paper chromatography, in 33 children with the nephrotic syndrome, based on an analysis of 196 urine samples. In a previous paper (*Acta paediat. (Uppsala)*, 1959, 48, 135; *Abstr. Wld Med.*, 1959, 26, 100) they stated that amino-acid excretion in nephrotic children is usually normal but that three types of hyperaminoaciduria had also been observed: Type 1, in which α -aminobutyric acid, valine, leucine, isoleucine, tyrosine, phenylalanine, and proline were particularly prominent (the so-called renal or "R-pattern", due to renal tubular insufficiency); Type 2, in which cystine, methionine, and taurine were prominent ("H-pattern"); and Type 3, in which there was a variable hyperaminoaciduria with varying excess of normal components—alanine, glutamic acid, serine, threonine, lysine, histidine, or arginine—together with excess amounts of amino-acids included in Types 1 and 2.

Of the 33 children 26 were given steroid therapy and the study was concentrated on 21 patients in whom at least one complete episode of the disease was observed to remission (18) or death (3). Altogether 30 nephrotic episodes (172 samples of urine) were studied in the 21 patients. Amino-

acid excretion was normal in 132 urine samples (19 patients). Of the 19 patients, 11, accounting for 84 of the urine samples, had hyperaminoaciduria at some other time while 8, accounting for 48 urine samples, had at no time an increased aminoaciduria. The 40 abnormal samples of urine were classified as follows: "R-pattern" 22 samples (corresponding to 6 patients), "H-pattern" 4 samples (corresponding to 2 patients), and Type 3, 14 samples (7 patients). Type-3 patterns were usually observed only after the administration of steroids and the "H-pattern" occurred in 2 patients who were also considered to be suffering from infective hepatitis.

The authors conclude that amino-acid excretion in the nephrotic syndrome is usually normal, that the "R-pattern" of hyperaminoaciduria occurs in approximately 20% of patients, that Type 3 is related to steroid therapy, and that none of the types of aminoaciduria has any particular diagnostic or prognostic significance.

[The paper contains tables giving extensive clinical, biochemical, and therapeutic data.]

Hewett A. Ellis

583. Steroid Therapy of the Idiopathic Nephrotic Syndrome in Children. (Steroidbehandling av idiopatisk nefrotisk syndrom hos barn)

H. C. SOMMERSCHILD. *Tidsskrift for den Norske Lægeforening* [T. norske Lægeforen.] 82, 672-675, May 15, 1962. 1 fig., 15 refs.

Thirty-five children with idiopathic nephrotic syndrome treated in two pediatric departments in Oslo during the period from 1950 to 1959 inclusive are reported on. The observation period averaged 4½ years, and all who became asymptomatic have been observed for at least 22 months after discontinuation of treatment. Symptoms of irreversible renal damage developed in one patient, and 4 patients died. Of the remaining cases, 22 became asymptomatic, while 8 are still under treatment. The results are satisfactory compared with those recently reported from other quarters. The best treatment seems to be administration of large doses of steroids, e.g., 30 to 60 mg. of prednisone daily for 3 or 4 weeks followed by maintenance therapy which probably should be continued for at least 12 months. The maintenance therapy may be postponed until the first relapse. It is usually given in the form of intermittent medication, with administration of the daily dosage mentioned above during 3 successive days each week. Some authors prefer continuous daily medication with smaller doses.

The immediate and symptomatic effect is usually good, but the final result of steroid treatment is still unknown. Prolonged observation, perhaps for 10 to 15 years, is required to allow definite conclusions as to the final result of steroid therapy as outlined above. The reduced mortality during the past ten years may—at least to a certain extent—be ascribable to other circumstances. The possibility of further improvement of the therapeutic results in idiopathic nephrotic syndrome in children seems to depend on a better understanding of the etiologic factors involved.—[Author's summary.]

Endocrinology

584. **A Simple Test for the Diagnosis of Diabetes Insipidus**
A. JADRESIC and J. MAIRA. *Lancet [Lancet]* 1, 402-403,
Feb. 24, 1962. 8 refs.

It was shown by Hickey and Hare (*J. clin. Invest.*, 1944, 23, 768) that diabetes insipidus could be distinguished from psychogenic polydipsia by the fact that urinary flow in normal subjects is reduced after the intravenous infusion of a saline solution, but not in patients with diabetes insipidus. The test was later modified by Carter and Robbins (*J. clin. Endocr.*, 1947, 7, 753), but the disadvantages of administering intravenous saline remained. The present authors have devised a simpler procedure and found it satisfactory. After undergoing a water-loading test the subject drinks one litre of 1% sodium chloride solution, the urine being collected for the next 2 hours and the amount expressed as a percentage of the intake.

The test was carried out on 20 normal subjects, 7 patients with diabetes insipidus, and a miscellaneous group including one patient with psychogenic polydipsia, all these subjects having previously shown a normal response to the water-loading test. In the saline test the normal subjects and most of the miscellaneous group including the case of psychogenic polydipsia excreted less than 25% of the intake, whereas in all the patients with diabetes insipidus the excretion amounted to over 65%, this level corresponding with that found after the water-loading test. Two patients with polyuria and hypercalciuria excreted 46% and 34% of the intake of saline solution. These results were similar to those obtained in the same patients with the test as modified by Carter and Robbins, so that the simpler procedure seems satisfactory as an aid in the diagnosis of diabetes insipidus.

Nancy Gough

585. **Diabetes Insipidus: the Influence of Chlorothiazide Therapy in Affected Children**

N. J. O'DOHERTY, J. ROSSER, and R. J. SLATER. *Canadian Medical Association Journal [Canad. med. Ass. J.]* 86, 559-567, March 31, 1962. 4 figs., 22 refs.

The antidiuretic effect of chlorothiazide and hydrochlorothiazide in 12 children and one adult suffering from diabetes insipidus was studied at the Hospital for Sick Children, Toronto. The children ranged in age from 4 months to 12 years; 5 of the children and the adult (the mother of one of the children) were suffering from nephrogenic diabetes insipidus and 7 children had vasopressin-insufficient diabetes insipidus. Chlorothiazide was given in an average daily dosage of 20 to 40 mg. per kg. body weight and hydrochlorothiazide in a dosage of 2 mg. per kg. daily. All except one child showed a response which was maximal within 3 days, but after about 7 days "resistance" developed in all but 3 patients. Toxic effects, which included pallor, apathy, and loss of consciousness, were observed in 2 patients. In one boy, aged 6 months, toxicity was noted when the dosage of chlorothiazide was increased to 70 mg. per kg. daily, and in the other patient, a boy of 2 years, toxic effects were associated with the development of a respiratory infection.

Chlorothiazide therapy resulted in a fall in the serum levels of sodium, potassium, and chloride, and a reduction of approximately 25% in fluid requirement and output. This improvement was not associated with an alteration in glomerular filtration as judged by the endogenous creatinine clearance values.

The possible mechanisms involved in the antidiuretic action of chlorothiazide are discussed. R. M. Todd

THYROID GLAND

586. **Non-toxic Diffuse Goitre: Factors Influencing the Effect of Thyroid Medication**

I. B. HALES, J. MYHILL, T. S. REEVE, and F. F. RUNDLE. *British Medical Journal [Brit. med. J.]* 1, 977-978, April 7, 1962. 2 figs., 6 refs.

Working at the Royal North Shore Hospital of Sydney, Australia, the authors devised a test aimed at predicting the effect of thyroid administration on non-toxic diffuse goitres. The uptake of radioactive iodine (^{131}I) by the thyroid gland one hour after an intravenous injection was determined. Then, either thyroxine (0.4 mg. daily for 21 days) or triiodothyronine (120 to 150 mg. daily for 7 days) was given and the ^{131}I uptake again measured. The ratio of the two determinations was termed the "suppression value". In fact in 71 (89%) of the 81 patients treated with thyroid preparations the size of the goitre was reduced; the suppressibility of iodine uptake was more marked in those who responded. The authors consider that the value of the suppressibility test can be improved by taking account of the size of the goitre.

M. C. G. Israëls

587. **Serum Proteins in Thyroid Disease**

W. W. BUCHANAN, D. A. KOUTRAS, W. D. ALEXANDER, and J. CROOKS. *British Medical Journal [Brit. med. J.]* 1, 979-982, April 7, 1962. 35 refs.

The serum protein values were determined by chemical and electrophoretic methods in 198 patients with various thyroid diseases at the Western Infirmary, Glasgow. The results are set out in a number of tables. The most striking findings were the raised γ -globulin level in autoimmune thyroiditis and the decreased serum albumin level in thyrotoxicosis.

M. C. G. Israëls

588. **The Clinical Significance of the Complement-fixation Test in Thyrotoxicosis**

W. W. BUCHANAN, D. A. KOUTRAS, J. CROOKS, W. D. ALEXANDER, W. BRASS, J. R. ANDERSON, R. B. GOUDIE, and K. G. GRAY. *Journal of Endocrinology [J. Endocr.]* 24, 115-125, 1962. 1 fig., 36 refs.

In this study from the University and Western Infirmary, Glasgow, on 468 patients with thyrotoxicosis, a significant correlation was found between the results of the complement-fixation test and the degree of round-cell infiltration in the thyroid gland, but not between the results of the test and

the incidence of reactions to antithyroid drugs. The incidence of positive reactions to the test was higher in patients with a family history of thyroid disease than in those without, and it is recommended that such patients should be treated initially with antithyroid drugs unless there is a definite indication for surgery.

G. B. West

589. **Circulatory Adaptation in Hyperthyroidism: Investigations by Cardiac Catheterization.** (Die Kreislaufanpassung bei Hyperthyreose: Untersuchungen mittels Herzkatheterismus)

A. UEHLINGER, F. SCHAUB, and A. BÜHLMANN. *Klinische Wochenschrift [Klin. Wschr.]* 40, 130-134, Feb. 1, 1962. 17 refs.

The haemodynamics in 8 patients with thyrotoxicosis were investigated by means of cardiac catheterization at the University Medical Clinic, Zürich, when the following factors were determined: oxygen uptake and consumption, arterio-venous oxygen differential, minute volume (cardiac index), the quotient of minute volume divided by oxygen uptake, stroke volume, pulmonary arterial pressure, and cardiac output.

The classic high output (that is, an increased quotient of minute volume/oxygen uptake) was noted in only 2 cases; other forms of circulatory adaptation were a high output with increased venous pressure, a relatively high output with unilaterally increased venous pressure, and a normal minute volume with normal venous pressure.

A. J. Karlish

PARATHYROID GLANDS

590. **Further Experience with Pancreatitis as a Diagnostic Clue to Hyperparathyroidism**

C. G. MISTER JR., W. M. KEYNES, and O. COPE. *New England Journal of Medicine [New Engl. J. Med.]* 266, 265-272, Feb. 8, 1962. Bibliography.

The authors review the increasing number of cases (at present totalling 51 reported in the world literature) in which pancreatitis occurs as a complication of hyperparathyroidism, to which they add 11 cases seen personally at the Massachusetts General Hospital, Boston. These patients formed part of a series of 155 proven cases of hyperparathyroidism seen at the hospital since 1950.

The sex and age distributions of the 62 patients did not differ significantly from that of all cases of hyperparathyroidism or from all cases of pancreatitis. In 17 cases the patient presented with pancreatitis and in 40 symptoms of pancreatitis preceded the diagnosis of hyperparathyroidism. Pancreatic calculi were present in 30 (81%) of the cases in which they were sought (including 4 of the authors' 11) and the majority of these were intraductal. All types of pancreatitis were found in the entire series, including 21 acute cases, 12 acute postoperative cases, and 13 recurrent acute cases. The commonest form, however, was chronic pancreatitis with pain, which occurred in 26 patients. Ten patients died as the result of acute pancreatitis. It was noted that correction of the hyperparathyroidism appears to remove or ameliorate the associated pancreatitis. The authors emphasize the importance of pancreatitis as a pointer to overactivity of the parathyroid glands and also the possibility of sudden and potentially fatal pancreatitis in patients with hyperparathyroidism. The serum calcium

levels may be depressed towards normal when acute pancreatitis supervenes in hyperparathyroidism. Pancreatic calculi or the finding of radiographic opacities in the area of the pancreas should arouse suspicion of hyperparathyroidism and these should be sought for in patients known to have parathyroid overactivity. Operation on the parathyroid glands should be the first and immediate line of treatment for the acute pancreatitis.

J. Warwick Buckler

591. **Plasma-alkaline-phosphatase in Normal Adults and in Patients with Primary Hyperparathyroidism**

C. E. DENT and C. M. HARPER. *Lancet [Lancet]* 1, 559-563, March 17, 1962. 3 figs., 25 refs.

In primary hyperparathyroidism the plasma alkaline-phosphatase levels are usually stated to be normal. In order to test this, the authors have compared the levels in a group of patients with hyperparathyroidism with those in a group of healthy subjects.

Plasma alkaline-phosphatase levels were estimated in 86 members of a hospital staff aged 17 to 55 years and compared with those in 70 cases of primary hyperparathyroidism confirmed at operation. The method of determining the plasma alkaline-phosphatase level was that of King, with the slight modification of incubating the "control" tubes simultaneously with the "test" tubes, in order to take into account any spontaneous hydrolysis of disodium phenylphosphate. The control subjects were active and healthy so far as simple questioning could elicit. The patients with hyperparathyroidism were the first 70 to be operated upon at University College Hospital, London, and were divided into two groups. The first group were "without bone disease" and showed no phalangeal subperiosteal erosion believed to be specific for osteitis fibrosa generalisata; many of the group showed bone changes due to other diseases, such as senile osteoporosis. The second group had "bone disease" with subperiosteal erosions in the phalanges or cystic changes elsewhere.

In the control group the mean plasma alkaline-phosphatase level in 38 females was 5.6 K.A. units and in 48 males it was 7.6 K.A. units. No correlation was found with height, weight, or age, and the authors suggest that the higher mean value in males may be related to the greater physical activity commonly undertaken by the male, this being the usual stimulus for increased bone formation. Of the patients with hyperparathyroidism those with bone disease had plasma alkaline-phosphatase levels at or above 16 K.A. units, which is well out of the normal range. In patients without radiological bone changes the level was in the normal range, although in the females in this group the level tended to be a little higher than the normal range for females.

The normal phosphatase level in cases of hyperparathyroidism without bone disease and the raised phosphatase level in cases with bone disease have been noted by Albright and Reifstein, but the present authors consider that the suggestion of these workers that the two forms result from a different dietary intake of calcium is quite untenable. They point out that they have described important clinical differences between the two forms of the disease (*Proc. roy. Soc. Med.*, 1959, 52, 993)—for instance, renal damage is more common with bone disease and cannot usually be explained as a complication of stone formation. They suggest that the two forms of the disease are usually clearly

distinguishable and rarely change into one another. Further work is required to determine whether the differences between the two forms can be immediately related to a metabolic or hormonal difference.

John Lister

DIABETES MELLITUS

592. Diabetes in East Pakistan

M. IBRAHIM. *British Medical Journal* [Brit. med. J.] 1, 837-839, March 24, 1962. 1 fig., 12 refs.

Between August, 1957, and December, 1959, a total of 894 patients suffering from diabetes mellitus were followed up at the Medical Research Centre, Dacca, East Pakistan, and the data concerning age and sex incidence of the disease, heredity, body weight, occupation and social status, incidence of ketosis and other complications, and therapeutic response to insulin and oral hypoglycaemic agents were analysed. Only 15 patients showed marked ketonuria and signs of precoma on withdrawal of insulin; in 30 there was temporary ketosis. Another interesting finding in this type of diabetes (referred to as "tropical" diabetes) was that the disease in 65% of the patients could be controlled with tolbutamide or chlorpropamide. It is believed that this type of tropical diabetes may be caused by a defect in the storage or release of liver glycogen rather than by deficient secretion of insulin.

A. I. Suchett-Kaye

593. Use of Diethylpropion in Obese Diabetic Patients

J. R. HENDON and S. URBACH. *Metabolism: Clinical and Experimental* [Metabolism] 11, 337-341, March, 1962. 18 refs.

Diethylpropion hydrochloride ("tenuate"; "tepanil") was given to 32 obese patients with mild diabetes, at Louisville General Hospital, Kentucky, in an attempt to effect reduction in their weight after standard low-calorie diets had failed to do so. All but one lost weight, the amount lost varying from 1 to 58 lb. (0.45 to 26.3 kg.) over periods ranging from 2 to 19 months. Only one patient, however, reached the desired weight, possibly because all the others proved to be irregular attenders; for this reason the authors feel unable to discuss the effect on the diabetes.

Side-effects were infrequent and mild. Some were considered to be manifestations of anxiety secondary to the reduced intake of food, rather than true side-effects of the drug, the probable mode of action of which may be to reduce the desire for food.

A. Gordon Beckett

594. Obesity and Diabetes in the Families of One Hundred Diabetic Children. (Obésité et diabète dans les antécédents de cent enfants diabétiques)

R. FRANÇOIS, J. SITE, and M. RONNIN. *Diabète* [Diabète (Le Raincy)] 10, 70-73, Feb. [received April], 1962. 8 refs.

A possible genetic relationship between the incidence of diabetes and obesity, the criterion for which is described, was studied by ascertaining the incidence of these conditions among the relatives of 100 children selected at random from a particular district near Lyons and representing a cross-section of all social groups and comparing it with that among the relatives of 100 known diabetic children attending the diabetic clinic. The incidence of obesity and diabetes was found to be greater in the latter group. The possible relationship between these two conditions was not, how-

ever, confirmed in regard to first cousins and their parents, but the numbers in these groups were small and the finding is therefore not conclusive either way. It is proposed to extend the study to include a wider range of relatives.

F. W. Chattaway

595. Phenethylbiguanide: Clinical Experiences with Timed-disintegration Capsules in Stable Diabetes Mellitus

R. S. RADDING, J. H. MCHENRY, W. B. NEELY, and F. R. LUMMIS JR. *Metabolism: Clinical and Experimental* [Metabolism] 11, 404-410, April, 1962. 4 refs.

A clinical trial of phenethylbiguanide given in timed-disintegration capsules is described in this paper from Hermann Hospital, Houston, Texas. The drug was administered in a dosage of 100 mg. daily to 82 patients with stable diabetes. In 25 of the patients the diabetes had previously been unsatisfactorily controlled by diet, 20 patients had received sulphonylureas, 27 had been treated with less than 50 units of insulin daily, and 10 had received over 50 units of insulin daily.

An effective response to phenethylbiguanide was obtained in 72 (88%) of the patients. In 21 out of 23 patients who had not responded to dietary management, phenethylbiguanide successfully controlled the diabetes. Of 20 patients previously given sulphonylureas 18 were treated successfully with phenethylbiguanide. Further, in those patients receiving insulin therapy a reduction in the insulin requirements was the rule. In none of the patients were gastro-intestinal side-effects sufficiently severe to call for cessation of treatment.

I. McLean Baird

596. Metformin in Treatment of Diabetes Mellitus

B. GÖTTLIEB and W. H. R. AULD. *British Medical Journal* [Brit. med. J.] 1, 680-682, March 10, 1962. 13 refs.

The effect of dimethylbiguanide (metformin) in diabetes mellitus was studied at St. Mary Abbots Hospital, London, in 39 patients (23 male and 16 female), 28 of whom were aged 50 years and over. In 20 cases insulin had previously been given, while in 6 the diabetes had been poorly controlled either with diet alone or with sulphonylurea derivatives; the remaining 13 were new cases.

All the patients were admitted to hospital for the first 2 or 3 weeks and then observed as out-patients. They received a diet of 2,000 Calories with 160 to 180 g. of carbohydrate. Metformin was given in a dosage of 0.5 g. 3 times a day and if necessary this was increased to 3 g. daily. After 6 months the diabetes was well controlled in 14 patients with metformin and in 6 with either tolbutamide or insulin in addition to metformin. In 10 patients the diabetes was not controlled by metformin and in 9 no assessment could be made. Side-effects—diarrhoea and nausea and vomiting—were responsible for failure in 2 cases; the drug also failed in 3 cases of diabetes due to pancreatic insufficiency.

Of 10 patients who had previously been ketotic only 4 had a good response for 6 months. Good control on metformin alone was not maintained by any of the 7 patients under 40 years of age. In several cases the maximum response was not observed until 12 to 14 days after treatment started.

The authors found in this small series that the best response to metformin was obtained in patients over the age of 40, who had no tendency to severe ketosis, did not have pancreatic diabetes, and weighed over 10 stones (63.5 kg.).

Charles Rolland

The Rheumatic Diseases

CHRONIC RHEUMATISM

597. Synovial Fluid Lipids in Rheumatoid and Osteoarthritis

A. C. CHUNG, J. R. SHANAHAN, and E. M. BROWN JR. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 176-183, April, 1962. 18 refs.

At Lankenau Hospital, Philadelphia, the authors estimated the cholesterol and phospholipid fractions in synovial fluid and serum from 20 patients with joint disease (rheumatoid arthritis in 10, osteoarthritis in 8, ankylosing spondylitis in one, and ileitis with arthritis in one). Many had had systemic steroid treatment and all except one had had intra-articular injections of steroid.

Analysis of 16 specimens of synovial fluid gave mean values for cholesterol, phospholipids, cholesterol:phospholipid ratio, and phosphatide that were not unlike normal serum values, but resembled β - rather than α -lipoprotein fractions. There was no clear difference between the figures for patients with rheumatoid arthritis and those for patients with osteoarthritis. Analyses of sera gave normal values, with again no difference between the patients with rheumatoid arthritis and those with osteoarthritis. Comparison of serum and synovial fluid taken simultaneously from the same patients showed that the fluid had rather lower cholesterol and phospholipid levels with a higher cholesterol:phospholipid ratio.

Cholesterol and phospholipids are presumably passed from serum to synovial fluid with some modification, but there is no information so far on the rate of passage or the influence of disease.

J. A. Cosh

598. Spontaneous Fractures in Rheumatoid Arthritis

R. HAIDER and G. STOREY. *British Medical Journal* [Brit. med. J.] 1, 1514-1516, June 2, 1962. 4 figs., 13 refs.

599. Pleurisy with Effusion in Rheumatoid Arthritis, with Reference to the Low Concentration of Glucose in Pleural Fluid

D. T. CARR and J. G. MAYNE. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 345-350, March, 1962. 2 figs., 13 refs.

This study comes from the Mayo Clinic and covers the years 1950-9, during which time about 1,000 cases of rheumatoid arthritis (R.A.) were seen, and among which there were 25 cases with pleural effusion; of the latter, 24 satisfied the criteria of the American Rheumatism Association for "definite" R.A. while the 25th was classified as "probable" R.A. Other possible causes for the effusions had been excluded. L.E. cells were demonstrated in the peripheral blood in 4 of the 24 patients tested, but rheumatoid factor was present in one of them and a typical olecranon rheumatoid nodule in another; the remaining 2 were regarded clinically as cases of R.A. in spite of the presence of L.E. cells.

The glucose concentration was determined in 10 of the 11 effusions tested and found to be very low (less than 17 mg.

per 100 ml.). In one case the oral administration of glucose raised the level in the blood but failed to affect the concentration in the effusion. In other diseases associated with pleural effusion glucose concentration in the effusion usually approximates to that in the blood. Pleural biopsy was carried out in 3 cases and showed a non-specific inflammatory reaction with no evidence of a rheumatoid nodule.

D. Preiskel

600. Metabolism of Tryptophan in Rheumatoid Arthritis

I. M. BETT. *Annals of the Rheumatic Diseases* [Ann. rheum. Dis.] 21, 63-69, March, 1962. 8 figs., 23 refs.

In an investigation at the Rheumatic Diseases Unit, Northern General Hospital, Edinburgh, in 25 patients and 25 controls the author confirmed the findings of other workers that the urinary excretion of 3-hydroxyanthranilic acid is increased in rheumatoid arthritis. This was shown not to be due to defective conjugation of the acid. Another metabolite of tryptophan, kynurenine, was also found to be excreted in increased amount in rheumatoid arthritis. When loading doses of tryptophan were given, increased excretion of 3-hydroxyanthranilic acid occurred in both patients with rheumatoid arthritis and controls. Kynurenine excretion was raised after ingestion of DL-, L-, or D-tryptophan, but a raised excretion of 3-hydroxyanthranilic acid was found only after L-tryptophan. The author briefly refers to the reported findings of increased excretion of 3-hydroxyanthranilic acid in a variety of diseases other than rheumatoid arthritis.

G. Loewi

601. Anemia in Rheumatoid Arthritis. I. Red Cell Survival Studies

A. BIECHL, J. E. STAPLETON, J. F. L. WOODBURY, and H. C. READ. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 401-405, March 3, 1962. 7 figs., 17 refs.

The survival of erythrocytes labelled with radioactive chromium (^{51}Cr) has been studied at Dalhousie University, Halifax, Nova Scotia, in 20 patients with rheumatoid arthritis and 20 normal subjects; 5 of the 10 men and 6 of the 10 women with arthritis were anaemic. No patient had splenomegaly or circulating L.E. (lupus erythematosus) cells, but 10 showed a positive result in the sheep cell agglutination test. In all patients both the direct and indirect Coombs tests were negative and the reticulocyte counts were within normal limits. The degree of the rheumatoid arthritis varied from mild to severe. [No mention is made of any concurrent therapy while the patients were undergoing these investigations.]

In the control group the mean erythrocyte survival time was 27 ± 3 days, while in the patients with rheumatoid arthritis it was 25.6 ± 3.19 days. Thus there was no significant difference in this respect between the two groups, for even in the severely affected patients the survival time was still 24.8 days. A slightly shortened erythrocyte life span was associated with severity of the disease rather than with the presence of anaemia or a positive sheep cell agglutination reaction. Only one patient showed significantly shortened

erythrocyte survival. From the results of "own" cell survival studies it is concluded that haemolysis is a relatively unimportant factor in the mechanism of the anaemia in rheumatoid arthritis.

In a review of previous investigations of this problem the authors show that in three of the larger reported series the number of cases with evidence of a shortened erythrocyte life span was small. They criticize Weinstein's data (*Blood*, 1959, 14, 950; *Abstr. Wld Med.*, 1960, 27, 213) and suggest that instead of 46% of his cases showing abnormality of red-cell survival only 15% did so, his criteria being too severe.

[They do not comment on the work of Richmond *et al.* (*Ann. rheum. Dis.*, 1961, 20, 133; *Abstr. Wld Med.*, 1961, 30, 397) in which these workers showed that normal donor cells have a significantly shortened life when transfused into patients with rheumatoid arthritis. Nor is it noted that the apparently normal length of survival of "own" cells in these patients has been explained by Mollison (1959) as being due to cells from patients with a chronic random destructive process being younger and more resistant to destruction than those from a normal person. The authors carried out no similar studies with normal cells on their patients.]

J. S. Malpas

COLLAGEN DISEASES

602. **The Arthritic Syndrome in Systemic Lupus Erythematosus.** (Суставной синдром при системной красной волчанке)

L. I. NESGOVOROVA. *Терapeuticкий Архив* [*Ter. Arkh.*] 34, 91-99, March, 1962. 2 figs., 24 refs.

Joint symptoms have been described in 80 to 90% of cases of lupus erythematosus from the time of Kaposi (1872). In the investigation here reported, out of 63 patients (60 women and 3 men) such symptoms were present in 62 (98.5%); in most they took the form of arthralgias of a fleeting and migratory type, but in others were often severe and persistent and in 16 cases excruciating and crippling. In 30 cases there was acute polyarthritis or peri-arthritis, involving chiefly the interphalangeal, metacarpo-phalangeal, radio-carpal, knee, and ankle joints, accompanied by marked involvement of the tendino-muscular tissues with contracture. The distribution was asymmetrical. These features, in conjunction with the skin lesions, are of diagnostic importance, as is the response to hormone therapy. L.E. cells were observed in the peripheral blood of 43 of these patients, and in the synovial fluid of the affected joints in one. The synovial fluid is of high viscosity and of low protein content; the reverse of the findings in rheumatoid arthritis.

L. Firman-Edwards

603. **Focal Scleroderma: Report of 19 Cases in Children.** E. M. CHAZEN, C. D. COOK, and J. COHEN. *Journal of Pediatrics* [*J. Pediat.*] 60, 385-393, March, 1962. 9 figs., 25 refs.

Focal or localized scleroderma (morphoea) is a rare disease in children, but because of cosmetic disfigurement or functional limitation it may cause considerable disability. The effect of the disease on the growth of 19 children is reviewed in this report from the Children's Hospital Medical Center, Boston, Massachusetts, and the Vanderbilt University Pediatric Service, Nashville, Tennessee, covering a 35-

year period. Girls were affected 3 times as often as boys. The age of onset of the condition was between 2 weeks and 11½ years of age, with an average of 5½ years. Trauma or intercurrent disease preceded the onset in 6 cases, but a causal relationship was not considered likely; there was no family history in any of the cases.

The lesions were discrete, elevated waxy plaques occasionally surrounded by a violaceous halo and varying in size from 0.5 cm. to 15 cm. They were predominantly unilateral. When the face or limbs were affected secondary atrophy of muscle and bone occurred. The degree of disability depended on the site affected; for example, 3 of the 9 children whose legs were affected were crippled. None of the children had evidence of systemic involvement, nor did the generalized disease develop later. Investigation of the blood and urine, electrocardiography, and barium-swallow studies gave normal results at all times.

The pathological changes in the skin were initially homogeneous swelling of the collagen fibres in the dermis, with fibrin and oedema between the bundles. Lymphocytes, plasma cells, and histiocytes were present. Degeneration of associated underlying muscle occurred early. Later in the disease there were atrophy of all the glandular elements of the skin, hyalinization of the collagen, and occasionally some calcification.

Discussing the differential diagnosis the authors point out that generalized or systemic scleroderma, in addition to being exceedingly rare in children, does not show the discrete areas of involvement of the focal condition, and visceral involvement is common. Dermatomyositis can be distinguished by the generalized muscle tenderness with malaise, fever, and peripheral oedema. Scleroedema affects the neck and is usually preceded by infection. In this very rare condition, pigmentation, calcification, and muscle atrophy do not occur and spontaneous remission is the rule. Fat necrosis and relapsing non-suppurative panniculitis (Weber-Christian syndrome) are other conditions which need to be considered.

In the treatment of focal scleroderma deep x-ray therapy and corticosteroids have proved unsuccessful. The effects of fasciotomy and of skin-grafting have been difficult to assess, but would not seem to be better than those of conservative orthopaedic methods with vigorous physiotherapy. The cause of the disease is unknown.

J. S. Malpas

604. **Relation of Positive L.E.-cell Preparations to Activity of Lupus Erythematosus and Corticosteroid Therapy**

N. F. ROTHFIELD and N. PACE. *New England Journal of Medicine* [*New Engl. J. Med.*] 266, 535-538, March 15, 1962. 1 fig., 13 refs.

The authors have analysed the results of a total of 583 L.E.-cell tests carried out at regular intervals on 25 patients with systemic lupus erythematosus who were followed up at Bellevue Hospital, New York, for an average period of 4½ years. For the whole group the incidence of positive reactions showed a statistically significant correlation with disease activity, whether or not the patients were receiving steroid therapy; positive results were obtained less frequently with more prolonged remissions. However, in individual patients this correlation was not always obvious. [Unfortunately, the authors did not study the intensity of the L.E.-cell phenomenon, which might have made the correlation more obvious.]

M. Wilkinson

Physical Medicine

605. **The Differential Diagnosis of Tremors. Their Physical Analysis by Ultrarapid Cinematography.** (Zur Differentialdiagnose des Tremors. Physikalische Analysen mit einer High-Speed-Kamera)

W. BIRKMAYER. *Deutsche Zeitschrift für Nervenheilkunde* [Dtsch. Z. Nervenheilk.] 183, 322-330, 1962. 3 figs., 9 refs.

Every method of investigating the structure of tremor opens new perspectives. In this study, carried out at the Lainz Neurological Clinic, Vienna, the author used a high-speed camera which could take 880 pictures per second, resulting, when the film was viewed, in a 55-fold slowing in motion; by means of suitable apparatus (described) it was possible to convert film-projection into linear representation of time and space. Investigations were carried out on one case each of Parkinson's disease, psychogenic (hysterical) tremor, and intention tremor.

It was found that movement in the first two conditions took place in one plane, whereas that due to intention tremor was in all three planes. Again, the energy or work output involved in Parkinsonian and psychogenic tremor was comparatively slight, but that in intention tremor was so high that it seemed impossible that this type of tremor could be maintained for any length of time. Parkinsonian tremor had a mean speed of 0.45 metre per second and intention tremor 2 m. per second, and accelerations ranging from 3.25 to 16.8 m. per second per second and from 11.25 to 104.6 m. per second per second respectively. It is difficult to differentiate Parkinsonian from psychogenic tremor, both of which are smooth and regular. The absolute arrhythmia in time and space seen in intention tremor seems to rule out any mechanism of spinal origin and suggests instead lack of inhibitory timing emanating from the higher co-ordinating centres.

[The original paper should be consulted for fuller details.]

D. Preiskel

606. **Corticosteroid Myopathy**

D. N. GOLDING, S. M. MURRAY, G. W. PEARCE, and M. THOMPSON. *Annals of Physical Medicine* [Ann. phys. Med.] 6, 171-177, Nov., 1961. 4 figs., 19 refs.

The authors describe, from the Royal Victoria Infirmary, Newcastle upon Tyne, the case histories of 5 patients who developed myopathy during prolonged corticosteroid therapy and of 2 patients suffering from rheumatoid arthritis who developed a similar myopathy without corticosteroid therapy, giving full clinical details.

There is evidence that an excess of circulating corticosteroid hormone, whether endogenous as a result of adrenal disease or exogenous from therapeutic administration, may produce a myopathy. If the myopathy occurs in association with a disease such as rheumatoid arthritis which itself causes muscle wasting, then the diagnosis is difficult. In 3 of the cases described the myopathy improved on withdrawal of the drug. It is suggested that the fluorine atom in some preparations such as dexamethasone may be the cause of the myopathy, and that therefore a change to a non-halogenated compound such as prednisone is to be recommended, with

gradual reduction of the dosage. In the present study muscle specimens examined under the electron microscope showed loss of myofilaments with fragmentation of their ends, and enlarged and functionless mitochondria in the sarcoplasmic areas between the broken myofilaments.

J. B. Millard

607. **Myopathies. Simultaneous Registration of the Agonist-Antagonist Couple by Global Electromyography. Anomalies Encountered in Myopathies and Therapeutic Consequences (U.T.P. and 2028 MD).** (Myopathies. Enregistrement simultané du couple musculaire agoniste-antagoniste par la méthode de l'électromyographie globale. Les anomalies rencontrées chez les myopathes, les conséquences thérapeutiques (U.T.P. et 2028 MD))

R. COIRAULT, A. D. HERSCHBERG, R. DAMASIO, J. RIGAL, B. ALLIOT, and H. BISSIÈRE. *Presse médicale* [Presse méd.] 69, 2373-2375, Dec. 2, 1961. 4 figs.

This work, which is based on a 2-year study of patients with myopathy, was carried out at the Military Hospital of Val-de-Grâce and the Centre de Saint-Jean-de-Dieu for young disabled boys, Paris. It was found early in the course of the study that conventional electromyographic examination of volitionally contracting muscle, using either a co-axial needle or surface electrodes, failed to throw light on observed phenomena of periods of arrest and relapse which occurred in myopathic patients during treatment with "U.T.P." [not explained]. The authors therefore investigated these cases by recording simultaneously the electromyographic response of one voluntarily contracting muscle and its antagonist. This technique demonstrated abnormality amounting to severe imbalance between the opposing muscles.

Over 30 patients with myopathy were examined regularly at intervals of 2 months, the biceps and triceps brachii being used as the agonist-antagonist pair of muscles. During elbow flexion (either free or resisted) abnormal and excessive triceps activity was observed, and during elbow extension abnormal biceps activity was noted. The authors claim that improvement in the patient's condition, as evidenced by decrease in this abnormal activity, occurs during treatment with U.T.P. only if this treatment is prolonged. Thus it is usually observed only after 10 to 12 months, but more rapid improvement may be obtained with 2028 MD (piperazine butyrophene).

Kenneth Tyler

608. **Brief Repeated Isometric Maximal Exercises: an Evaluation by Integrative Electromyography**

W. T. LIBERSON, M. DONDEY, and M. M. ASA. *American Journal of Physical Medicine* [Amer. J. phys. Med.] 41, 3-14, Feb. [received April], 1962. 11 figs., 13 refs.

Previous work on muscle physiology is discussed, with special reference to single or repeated isometric exercises to increase muscle efficiency, in this paper from Connecticut State Veterans Hospital, Rocky Hill. It is suggested that there may be an optimum position for a joint to give maximum muscle exercise and this may account for the varying

results when isotonic and isometric exercises are compared. The authors have investigated this problem, using an integrative electromyogram, which is obtained by the summation of muscle spike potentials the decay of which is electronically delayed. The triceps, biceps, deltoid, and gastrocnemius muscles were studied while acting against a tensiometer or isometric strain gauge myograph, and a comparative assessment was made with the muscle and joint in various positions. The electrogenesis produced during maximal isometric exercises was four times as high as during progressive resistance exercises. The triceps, biceps, and deltoid muscles showed a fall in electrogenesis with the muscle in the shortest position, but the biceps showed a maximum when the elbow was at 90 degrees. In the case of the gastrocnemius muscle electrogenesis was maximum when the muscle was shortened. The findings are discussed in relation to other work, and it is stressed that the mechanical advantage of various joint positions is important and the bulk of muscle under the recording electrode, which alters in some muscles more than others, may affect the results.

In all the experiments the electrical output and mechanical output were parallel except with the gastrocnemius muscle, but the many unknown factors make an interpretation difficult. Electrogenesis showed no definite evidence to suggest maximum activation at any joint angle, but it seems that isometric exercises should not be carried out with the muscle shortened and at a mechanical disadvantage. Maximum brief isometric exercises were more efficient than progressive resistance exercises.

J. B. Millard

609. Measurement of the Stretch Reflex Response as an Approach to the Objective Evaluation of a Spasticity
O. E. MIGLIETTA and M. LOWENTHAL. *Archives of Physical Medicine and Rehabilitation* [Arch. phys. Med.] 43, 62-68, Feb. [received April], 1962. 2 figs., 6 refs.

The authors describe from New York Medical College a simple objective method of eliciting the patellar stretch reflex and recording the response on a standard electromyograph. The technique is to seat the subject with the knee pendant at a right angle and tap the patellar tendon with an electrically activated hammer, which gives a blow of constant force. The hammer consists of the moving magnetic core of a direct-current coil applied at right-angles to the patellar tendon at a fixed distance. A single sweep of the electromyograph is synchronized with the patellar tap. Metal disk electrodes are attached in pairs 2 cm. apart along the quadriceps muscle belly to record the maximum action potential. This technique produces a biphasic action potential whose amplitude is dependent on the number of reflexly activated motor units. In practice the maximum response from several paired electrodes is recorded. In patients with spastic conditions the response is increased and can be reproduced with a variation of between 10 and 15% over several weeks. The whole test takes about 15 minutes to carry out.

The results of a trial of several muscle relaxant drugs given over 7 to 10 days and compared with a placebo are reported, the amplitude of the action potential measured in microvolts being used for comparison. No patient receiving the placebo showed a change, and in all the others there was a reduction in the stretch reflex response. Another 3-week trial of 71 patients with hemiplegia, disseminated

sclerosis, or paraplegia who were given various muscle relaxants is also reported. In these cases there was an average reduction in the stretch reflexes of 46.7%, only 6 patients showing no reduction compared with pre-medication recordings. It is suggested that this type of test is useful to enable the clinician to regulate the dose of a therapeutic agent for each patient and measure the duration of the response to a muscle relaxant.

J. B. Millard

610. Comparison of Relative Heating Patterns Produced in Tissues by Exposure to Microwave Energy at Frequencies of 2,450 and 900 Megacycles

J. F. LEHMANN, A. W. GUY, V. C. JOHNSTON, G. D. BRUNNER, and J. W. BELL. *Archives of Physical Medicine and Rehabilitation* [Arch. phys. Med.] 43, 69-76, Feb. [received April], 1962. 8 figs., 8 refs.

In the study here reported from the University of Washington School of Medicine, Seattle, the authors heated the thighs of recently slaughtered pigs, using rectangular waveguides with a slotted centre section connected to either a commercial generator with a maximum output of 100 watts from a magnetron tube as the 2,450-megacycle source, or an Air Force radar transmitter with a maximum output of 50 watts as the 900-megacycle source. Readings were taken with a bolometer probe and a microwave power meter, and the temperature distribution was measured with silver-plated stainless-steel needle thermocouples placed parallel to the magnetic field vector. Theoretical considerations are given in detail.

It was found that greater heating of subcutaneous fat occurred with the higher frequency, but that depth of penetration was greater at the frequency of 900 megacycles, so that this frequency gives better deep heating. These results confirm the theoretical calculations, though it is stressed that they have not yet been confirmed *in vivo*. It is suggested that microwaves applied to obese patients will mainly heat the fat, but in normal persons the frequency of 900 megacycles would give greatest heating in muscles, especially those of the deeper layers.

J. B. Millard

611. Action Potentials from Single Motor Units in Human Muscle

H. FLECK. *Archives of Physical Medicine and Rehabilitation* [Arch. phys. Med.] 43, 99-107, March, 1962. 6 figs., 26 refs.

This paper attempts to analyse experimentally the fusion potential of a single human motor unit. To this end the various types of electrode are presented and their parameters are discussed. Two new types of electrode are introduced. With the conventional coaxial electrode, mutation of the potential's configuration is shown to occur on rotation of the needle. This demonstrates that some of the records found in the literature are due to rotation or skewed position of the recording surface with respect to the course of the muscle fibers. A quadriphasic potential was obtained with the "differential" electrode and two such potentials with the "double differential" electrode. The possible uses of such electrodes are discussed in the differential diagnosis of neuromuscular disorders. Standardization of electrodes to facilitate communication between researchers is advocated, as well as the proper care of the electrodes as precision tools in the study of dynamic events in the muscle.—[Author's summary.]

Neurology and Neurosurgery

612. **Observations on the Water Balance in Unconscious or Clouded Patients treated with Diuretics.** (Beobachtungen zum Problem des Wasserhaushaltes bei der Behandlung bewusstseinsgetrübter Patienten mit Diureticis) K. SCHMIDT. *Archiv für Psychiatrie und Nervenkrankheiten* [Arch. Psychiat. Nervenkr.] 202, 649-656, 1962. 2 figs., 24 refs.

Cerebral conditions of all kinds very often necessitate artificial feeding of the patient, since gastric atonia, unconsciousness, or paralysis of the muscles of deglutition may make normal feeding impossible. At the same time in these cases, in order to reduce cerebral oedema, powerful diuretics are often given. While renal function remains intact dehydration can easily be detected by urinary tests, but if diuretics are given this is no longer possible. In this study of 40 unconscious neurosurgical patients, all were shown by haematocrit estimations to be markedly dehydrated, even after a single dose of a diuretic drug. In a control group of conscious patients who were also being artificially fed the same dose of the diuretic produced only a slight rise in the haematocrit value, since these patients were able to compensate for the excessive fluid loss by increasing their fluid intake in response to thirst.

J. Hoenig

613. **Difficulties in the Diagnosis of Papilloedema.** (Über die Schwierigkeiten einer richtigen Diagnose der Stauungspapille) J. SOBAŃSKI and I. SWIETLICKO. *Klinische Monatsblätter für Augenheilkunde* [Klin. Mbl. Augenheilk.] 140, 71-75, Feb., 1962. 18 refs.

The differential diagnosis of papilloedema, optic neuritis, and pseudo-papillitis is discussed with special reference to the ratio of the diastolic pressure in the retinal artery to that in the retinal vein. If the ratio is normal, that is, 1:2 or 1:3, papilloedema can be excluded, even if the optic disk is red, indistinctly delimited, and prominent, when incipient papillitis should be suspected. If a change in the ratio is produced by a lowering of the diastolic pressure in the central retinal artery, papilloedema may be assumed as an expression of local or general hypotension. A change in the ratio caused by an increase in the diastolic venous pressure may indicate either papilloedema due to increased intracranial pressure or bilateral retrobulbar neuritis; in such cases good vision will favour the diagnosis of papilloedema, while lowered visual acuity points to neuritis. In a few cases the final decision may have to depend on the exclusion, by lumbar puncture, of an intracranial lesion.

L. Wittels

614. **The Musculotendinous (Shoulder Cuff) Syndrome. The Value of the Electromyogram in Its Differential Diagnosis** A. A. MARINACCI and J. H. LINDHEIMER. *Bulletin of the Los Angeles Neurological Society* [Bull. Los Angeles neurol. Soc.] 27, 14-21, March [received May], 1962. 9 refs.

Writing from the County Hospital, Los Angeles, the authors first describe the anatomy of the musculotendinous cuff of the shoulder joint and then discuss the pathology of

the shoulder cuff syndrome and its differential diagnosis. Case histories are presented to illustrate how various lesions, such as tumours or prolapse of the intervertebral disk in the region of cord segments C5 and C6, injuries to the upper trunk of the brachial plexus or to the suprascapular nerve or median nerve, and several other conditions, can simulate the shoulder cuff syndrome. The electromyogram gives great diagnostic help, since it is always normal in the true shoulder cuff syndrome, but shows characteristic patterns in the other conditions mentioned above.

Janet Q. Ballantine

615. **Electroencephalographic Changes in Psychomotor Epilepsy.** (EEG-Veränderungen bei der psychomotorischen Epilepsie)

W. CHRISTIAN. *Deutsche Zeitschrift für Nervenheilkunde* [Dtsch. Z. Nervenheilk.] 183, 218-244, 1962. 14 figs., 29 refs.

The author examined the electroencephalograms (EEG) of 712 patients with psychomotor epilepsy seen at the University Neurological Clinic, Heidelberg [see Abstract 621], in an attempt to correlate the clinical picture with the EEG findings. In 548 cases 3 or more EEG recordings were obtained and these are analysed in detail. The EEG was found to be normal in 12% of all patients.

In patients with the oral type of seizure abnormalities were present mostly over the medio-basal part of the temporal lobe; they were localized and nearly always bilateral. In those with the adverbial type widespread abnormalities in the EEG were found in 80% in the contralateral hemisphere, in 15% in the ipsilateral hemisphere, and in 5% bilaterally; more localized parietal abnormalities were not infrequently found in patients with vestibular aura. In those with the dysphasic type, if an abnormality was present, it was always on the left side in the posterior temporal area. In the "pure psychomotor seizures" extra-temporal foci were quite frequent. The findings in EEGs recorded during and between attacks are discussed in detail. It is pointed out that regular 3 c.p.s. spike-and-wave complexes occur in young persons with psychomotor epilepsy. A certain degree of correlation between the clinical types as outlined by Hallen and the EEG abnormalities was established.

H. S. Schuita

616. **Periodic Fever, an Entity. A Collection of 52 Cases** H. A. REIMANN. *American Journal of the Medical Sciences* [Amer. J. med. Sci.] 243, 162-174, Feb., 1962. 9 figs., 41 refs.

In this paper from Hahnemann Medical College and Hospital, Philadelphia, are surveyed 52 cases of fever recurring periodically, of which a number were collected from the literature and some were seen personally by the author. The bouts of illness recur in often predictable cycles of hours, days, weeks, or months; a tendency for them to recur in cycles of 7 days or multiples of 7 days is noted. Fever is the chief feature, with chills, sweating, aching, and malaise. Evidence of a disturbed autonomic or vasomotor system differed from case to case and leucocytic and plasma protein

responses were variable. There was an aberrant electroencephalogram in 8 of the 10 cases in which this was recorded. Temporary intermissions can occur, sometimes with intercurrent infection, and the bouts of fever ceased completely in 6 cases. Five patients died apparently from the condition, one patient died from amyloidosis, and 7 from other causes. The condition is hereditary and may begin at any age. No cause or effective treatment has been found.

The condition has many similarities to other periodic diseases, but appears to be a separate entity. It does not occur in families with a history of periodic peritonitis, but has occurred in those with a history of migraine. The site of origin seems to be the brain, but the nature of the disorder is unknown.

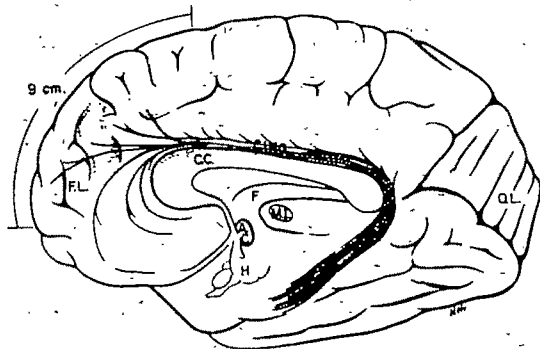
E. H. Johnson

BRAIN AND MENINGES

617. Pain "Relief" by Frontal Cingulumotomy

E. L. FOLTZ and L. E. WHITE JR. *Journal of Neurosurgery* [J. Neurosurg.] 19, 89-100, Feb., 1962. 5 figs., 35 refs.

The authors describe the results of treatment of intractable pain by division of the cingulum, a multisynaptic fibre pathway connecting the medial frontal cortex and anterior thalamic nuclei with the hippocampal formation (see diagram). These fibres lie deep (that is, lateral) to the cingulate gyrus and can be electrocoagulated through frontal burr holes without performing a cinglectomy.



Anatomical location of frontal cingulum fasciculus, CING. = cingulum; C.C. = corpus callosum; F.L. = frontal lobe.

The operation was performed on 16 patients who had in common a complaint of prolonged pain with a marked emotional element which had not been relieved by other methods. Five patients were classified as suffering from psychogenic pain, and all of these showed good results. "Excellent" results were obtained in one patient with causalgia and one with emotionally induced angina. Good results were also obtained in patients with organic pain from neoplastic disease. An interesting result of the operation was the effect on narcotic addiction; 14 of 16 patients were addicted before the operation, and abrupt withdrawal of the drug after it resulted in no withdrawal syndrome in 9 cases and only minimal symptoms in the other 5. Adequate clinical results from this operation were achieved even in unilateral lesions.

The authors conclude that cingulumotomy is a simple and safe type of leucotomy for relief of pain, and they suggest further approaches to the problem of selection of patients.

J. B. Stanton

618. Studies of Thyroid Function with Radioactive Iodine in Patients with Lesions of the Diencephalon. (Исследование функции щитовидной железы, радиоактивным йодом (I^{131}) при поражениях промежуточного мозга) L. A. EROFEEV and G. A. SEVOST'YANOVA. *Советская Медицина* [Sovetsk. Med.] 25, 73-78, March, 1962. 1 fig., 11 refs.

An assessment of thyroid function by means of radioactive iodine (I^{131}) was made on 50 patients suffering from symptoms of injury of the diencephalon, these including neurovascular paroxysms, temperature disturbances, impaired carbohydrate and fat metabolism, Cushing's syndrome, adiposo-genital dystrophy, and in some cases thyrotoxic symptoms not responding to specific therapy and often accompanied by some features suggesting hypothyroidism. Of the 50 patients, 21 showed normal curves of iodine uptake, except that in 11 of them the percentage uptake exceeded 10 (up to 17.5% in one case); 16 gave irregular curves with delayed saturation, reaching the maximum uptake level only after 48 hours, while 13 showed very low uptake levels (less than 1% in most cases). The dose of I^{131} was 1 to 2 μ c. in 25 ml. of water to fasting patients early in the morning; estimations of thyroid uptake were made hourly with a Geiger counter for 4 hours, then at 24 hours, and often again at 48 hours. The distribution curves in the above three groups were not related to the age or sex of the patient, except that the second group were all aged over 20 and only one was over 40. The authors conclude that in lesions of the diencephalon there is frequently impairment of thyroid function which does not respond to direct treatment for thyrotoxicosis or hypothyroidism, and may manifest itself by symptoms of either condition.

L. Firman-Edwards

619. Tumours of the Precentral Region with "Posterior Cerebral Fossa" Symptomatology. (Tumeurs de la région précentrale à symptomatologie de "fosse cérébrale postérieure")

J. RADERMECKER and G. MOYA. *Neurochirurgia* [Neurochirurgia (Stuttg.)] 4, 182-193, Feb., 1962. 4 figs., 22 refs.

In this paper from the Institut Bunge, Antwerp, detailed case histories are presented of 3 patients in whom the presence of false localizing signs suggestive of a neoplasm in the posterior fossa initially obscured the true site of the tumour, namely, the precentral area. The cerebellar signs—dysmetria, adiadochokinesis, hypotonia, and a wide-based gait—were associated in these cases with a raised intracranial pressure and papilloedema. The clinical problems and the relative values of electroencephalography, ventriculography, and angiography in helping to clarify the diagnosis in these cases are discussed. The significance of raised intracranial pressure in producing cerebellar signs by causing tentorial and foramen magnum herniation is stressed. In the present cases the tumours were situated in the upper part of the motor cortex or in the parasagittal region, and the authors discuss the possible role of direct reciprocal connexions between this part of the cortex and the cerebellum in producing the cerebellar signs, particularly in cases in which the intracranial pressure is not raised.

J. B. Stanton

620. **Treatment of Hydrocephalus in Infants by Ventriculo-cardiac Anastomosis: with Reference to 7 Cases.** (Traitement de l'hydrocéphalie du nourrisson par anastomose ventriculo-cardiaque. A propos de 7 observations)

P. GIRAUD, J. COIGNET, J. BONNAL, and J. ESPINAS. *Archives françaises de pédiatrie* [Arch. franç. Pédiat.] 19, 5-16, Jan. [received April], 1962. 4 figs.

A shunt between the lateral ventricle and the right atrium through the internal jugular vein, incorporating a Spitz-Holter valve, was performed in 7 hydrocephalic infants aged 2 to 21 months, between April, 1959, and August, 1961, at the Hôpital de la Conception, Marseilles; in none of the cases was the hydrocephalus associated with spina bifida cystica.

There were 3 cases of toxoplasmic encephalitis and 2 of basal arachnoiditis; the aetiology in the other 2 cases was not known. Three children died at various times after the operation, but 2 were in good condition and 2 in very good condition at the time of reporting [which could be only a matter of weeks after operation in 2 cases]. One toxoplasmic child appeared to be physically and mentally normal at 2½ years of age, that is, 2 years after this operation. Revision of the shunt was necessary in 2 cases, because of blockage of the jugular catheter in one (in which the outcome was good) and because of *Proteus morganii* septicaemia in the other child, who died. The authors consider that this method of treatment is a great advance over previous techniques for the drainage of superfluous cerebrospinal fluid.

John Lorber

621. **The Differentiation of Psychomotor Attacks into Clinical Forms.** (Zur Differenzierung der psychomotorischen Anfälle in klinische Formen)

O. HALLEN. *Deutsche Zeitschrift für Nervenheilkunde* [Dtsch. Z. Nervenheilk.] 183, 199-217, 1962. 41 refs.

In this clinical study of psychomotor seizures, the author reviews 712 such cases seen at the University Neurological Clinic, Heidelberg. The biphasic nature of these seizures is emphasized, the attack being preceded by an aura and followed by a state of confusion. Clinically the attacks can be divided into 4 groups as follows. (1) The oral type (520 cases) in which sensory or motor aspects of feeding are regarded as the nucleus of the fit; this is sometimes preceded by a dreamy state, and followed by a period of confusion during which the patients appear to attempt to re-orientate themselves in their surroundings or perform stereotyped actions or movements. (2) The adversive type (48 patients), manifested by turning of the head, the trunk, or the whole body to one side, preceded by a vertiginous, visual, or acoustic aura and followed by a state of confusion, during which the turning movements are frequently elaborated. (3) The dysphasic or vocalizing type (57 cases), characterized by verbal or vocal automatisms; a high percentage of these patients have an aura consisting of fear, but acoustic, olfactory, or epigastric auras may also occur. (4) Pure psychomotor attacks (87 cases), with scratching, wiping, or stamping movements, often preceded by a dreamy state or occasionally by an epigastric or olfactory aura.

The author draws attention to the fact that the variations of the symptoms are manifold, whereas the electrical abnormalities appear to be relatively constant [see Abstract 615]. It is pointed out that the seizures are not always due to focal disturbances in the temporal lobes.

H. S. Schutta

622. **Seizures Induced by Movement**

W. A. LISHMAN, C. P. SYMONDS, C. W. M. WHITTY, and R. G. WILLISON. *Brain* [Brain] 85, 93-108, March, 1962. 13 refs.

In this paper from the Radcliffe Infirmary, Oxford, 7 patients are described in whom sudden voluntary movements produced stereotyped attacks of additional spasm or athetosis. The attacks occurred frequently and usually started in childhood. They were constantly precipitated by sudden movements and in some of the patients they could be induced voluntarily. The spasm might involve the whole body but was commonly localized to one limb or one side, sometimes with a preliminary sensory aura in the affected limb. Consciousness was never lost. Clonic movements were absent and each attack usually lasted less than one minute. In 5 cases electroencephalograms showed abnormalities either in the resting record or on overbreathing. Anticonvulsants reduced the frequency and severity of the attacks in 6 cases, abolishing them completely in one.

The authors discuss the aetiology, but find no evidence that electrolyte imbalance plays a part. They conclude that the attacks represent a reflex epilepsy involving the basal ganglia, in which the sensory stimulus consists of afferent impulses from proprioceptors in muscles and tendons. The possibility that cortical or subcortical activity particularly associated with the initiation of voluntary movement may be a factor is also mentioned.

J. B. Stanton

623. **Effectiveness of Stereotaxicotomy in Treatment of Parkinson's Disease**

C. A. FAGER. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 703-707, March 3, 1962. 2 figs., 11 refs.

Observations are reported from the Lahey Clinic, Boston, on 45 patients with Parkinson's disease in whom lesions were produced in the globus pallidus and thalamocapsular regions by stereotaxic methods for the purpose of alleviating tremor and rigidity. The numerous surgical procedures at present employed in the treatment of Parkinsonism fall broadly into two general groups: (1) true stereotaxic procedures involving complicated electrode placements, depth recordings, and stimulations; and (2) non-stereotaxic insertion of cannulae by trial-and-error methods, which, however, leave the operator with a sense of insecurity and inadequacy, although they can produce excellent results in very experienced hands. The author has used a simplified form of stereotaxic instrument, the McPherson, which was first described in 1954 by Mark *et al.* (*Amer. J. Roentgenol.*, 71, 435); it combines simplicity with reasonable accuracy and can be adapted for use with a balloon cannula.

Of 58 chemical lesions produced in the thalamocapsular or globus pallidus region, excellent or good results were obtained in 24; in the remainder, however, there was no significant improvement. This latter group included a number of patients with far-advanced disease, who it is now realized are not likely to benefit from the operation. However, there were a certain number of failures even in patients with unilateral symptoms. The author found discrete globus pallidus lesions did not abolish tremor, but did in some instances relieve rigidity. Thalamic lesions produced at the point where the ventrolateral nucleus borders the posterior limb of the internal capsule proved most effective in alleviating both tremor and rigidity.

J. V. Crawford

Psychiatry

624. Evidence for a Congenital Factor in Maladjustment and Delinquency

D. H. STOTT. *American Journal of Psychiatry* [Amer. J. Psychiat.] 118, 781-794, March, 1962. 5 figs., 23 refs.

The author reports, from the University of Glasgow, that a re-calculation of the official figures collected by Wilkins for boys and youths appearing before the courts in England and Wales between 1949 and 1957 suggests that among juvenile offenders aged 14 to 21 there is a sharp peak of proneness to delinquency among those born in 1935-7. In contrast, for younger offenders aged 8 to 13, the peak occurs in the generation born during the worst of the war years, that is, 1939-43. The author interprets the first peak as due to the "Teddy boy" fashions of 1954-7, which may have led to more stringent police action against older youths at that time. He interprets the second peak as due to congenital damage caused by maternal stress during pregnancy, such damage being most likely to show itself in behaviour disturbance at an early age.

The author's own study of boys on probation in Glasgow in 1957 indicated an association between behaviour disturbance and physical inadequacy. The criterion for maladjustment was the score on the Bristol Social Adjustment Guides filled in by school teachers, while the data on health were supplied by the school medical service. Among the probationers, and also among a control group, a high score on maladjustment was found to be significantly associated with increased respiratory and other ailments, and also with physical defects and anomalies of growth or stature. The associations held good among probationers from homes rated as adequate by the probation officers, and they also held good after the exclusion of depressed children. Boys whose behaviour suggested compensation for feelings of frustration and inadequacy actually showed less than average physical defect. The author concludes that the most plausible explanation rests in an underlying congenital factor accounting for both the somatic defect and the impairment of nervous control of behaviour.

D. J. West

625. Ulcerative Colitis and the Psyche. (Colitis ulcerosa and Psyche)

H. FEIEREIS, K. KAMROWSKI, and H. G. ROHRMOSER. *Archiv für Psychiatrie und Nervenkrankheiten* [Arch. Psychiat. Nervenkr.] 202, 657-677, 1962. Bibliography.

At the City Hospital, Lübeck, Germany, 53 patients (17 men and 36 women) with ulcerative colitis were psychiatrically investigated and treated with relaxation exercises. Psychiatric abnormalities were found in 51 of the patients and these could be divided into the following four groups: (1) constitutional abnormalities, 18 patients (13 with subnormality and 5 with personality disorders); (2) neurotic personalities, with definite conflicts with their environment (17 patients); (3) neurotic personalities without obvious conflicts (5 patients); and (4) those predominantly in conflict with the environment without a neurotic personality structure (11 patients). A family history of personality disorder was found only in 6 patients.

The authors conclude [without referring to any controls] that there is an excess of psychiatric abnormalities in patients with this disease. Thus, 36 of the 51 patients showed acute conflict situations and the precipitating circumstances were usually some event arousing feelings of insecurity in the patient (such as uprooting, loss of a home, or loss of a relative). The ulcerative colitis is thus "an organic response to intrapsychic tensions" which the patient tries to cover up under a cloak of apparent contentedness. Most of the present patients were successfully treated by means of relaxation exercises, hypnosis, and discussion of their problems, and in only a few resistant cases did it become necessary to resort to psycho-analysis.

J. Hoenig

626. Hysteria—the Stability and Usefulness of Clinical Criteria. A Quantitative Study Based on a Follow-up Period of Six to Eight Years in 39 Patients

M. J. PERLEY and S. B. GUZE. *New England Journal of Medicine* [New Engl. J. Med.] 266, 421-426, March 1, 1962. 17 refs.

The results are reported of a follow-up study in 1960 of 39 out of 46 patients in whom hysteria had been diagnosed at Washington University Psychiatric Clinic, St. Louis, Missouri, in 1952 or the first half of 1954. On the basis of the initial history in each case a retrospective diagnosis was made of "hysteria" in 17 cases, "possible hysteria" in 11, and "no hysteria" in 11, the following criteria being applied: (1) a dramatic or complicated medical history beginning before the age of 35 years; (2) the presence of a minimum of 15 symptoms for hysteria (fewer for possible hysteria) distributed among at least 9 of 10 groups listing a total of 56 symptoms; and (3) the presence of symptoms which could not be explained by any other diagnosis. One of the 10 groups of symptoms included "blindness, paralysis, anaesthesia, aphonia, fits or convulsions, unconsciousness, amnesia, deafness, hallucinations, or urinary retention". The other 9 groups listed symptoms commonly found in psychoneurotic patients. At the follow-up interview the same diagnostic criteria were applied, except that the boundary between possible hysteria and hysteria was set at 25 instead of 15 of the 56 symptoms.

Of the 28 patients with a retrospective diagnosis of hysteria or possible hysteria, only 3 were considered to have no hysteria at the follow-up interview (the condition in these patients being diagnosed respectively as anxiety neurosis, chronic alcoholism, and possible manic-depressive disease). The diagnosis of no hysteria was confirmed in all 11 patients in whom such a diagnosis was made retrospectively. Of the 2 males in this group, one had a meningioma while the other was a schizophrenic. Of the females, 2 suffered from chronic alcoholism, one from anxiety neurosis, one from obsessional neurosis, and 3 from possible manic-depressive disease; in 2 the condition remained undiagnosed.

The authors conclude that it is possible to define a syndrome, hysteria, which occurs predominantly or exclusively in women and remains essentially unchanged over many years; further, that the use of rigorous criteria enables this

diagnosis to be rejected in many patients who subsequently prove to have other clinical disorders.

B. S. Meldrum

627. A Survey of Sex-chromosome Abnormalities among 4514 Mental Defectives

N. MACLEAN, J. M. MITCHELL, D. G. HARDEN, J. WILLIAMS, P. A. JACOBS, K. A. BUCKTON, A. G. BAIKIE, W. M. COURT BROWN, J. A. MCBRIDE, J. A. STRONG, H. G. CLOSE, and D. C. JONES. *Lancet [Lancet]* 1, 293-296, Feb. 10, 1962. 18 refs.

A survey was made at the Western General Hospital, Edinburgh, of the nuclear sex of 4,514 mental defectives from 15 institutions—one in England and 14 in Scotland. Of the 4,514 buccal smears examined, 1,056 were stained by Barr's modification of Klinger and Ludwig's method and the remainder by Ross's technique.

Of 2,607 males, 28 (10.7 per 1,000) were chromatin-positive, 23 with a single sex-chromatin body, 4 with some cells with 2 bodies, and one with some cells with 3 bodies. XXY complement was present in 17 (6.5 per 1,000), XXXY in 4 (1.5 per 1,000), XXXYY in 2 (0.8 per 1,000), and 5 were mosaics (1.9 per 1,000). Among 1,907 females, 8 (4.2 per 1,000) showed 2 sex-chromatin bodies and one was chromatin-negative; XXX sex-chromosome complement was present in 7 cases and mosaic XX/XXX in one. Other series reported in the literature are added to the present series and, in males, rates of 8.1 per 1,000 for a single body and 9.5 per 1,000 for all types of abnormal nuclear sex are obtained. Comparison of these figures with those of surveys of babies shows that the association of major mental deficiency and sex-chromosome abnormality is almost certainly not due to chance ($P < 0.001$). With data obtained from boys attending schools for the educationally subnormal ($P < 0.02$), the findings of sex-chromosome abnormality ranged from 23.8 to 4.5 per 1,000. Over-all figures for females give an incidence of XXX complement of 4.5 per 1,000, comparison with figures for female babies indicating the frequency to be significantly greater in mental defectives ($P < 0.001$). For females with XO complement the incidence was 0.5 per 1,000, but the limited data available suggest that these women are not appreciably mentally handicapped.

[The authors assume that "because the subjects were inmates of mental-defective institutions, it is reasonable to classify them under the heading of 'major mental defect'". In the opinion of the abstracter this is incorrect. Many patients with minor mental defect are in institutions because there are no homes, no relations, or no guardians willing to accept them.]

G. de M. Rudolf

628. Experiences with a New Antidepressant—Amitriptyline

M. ROSENBAUM and S. GERSHON. *Medical Journal of Australia [Med. J. Aust.]* 1, 321-325, March 3, 1962. 1 fig., 12 refs.

This paper from Prince Henry's Hospital, Melbourne, describes an uncontrolled trial of amitriptyline, a drug structurally related to imipramine and chlorpromazine, on a mixed group of 50 out-patients with depressive symptoms; the starting dose of 25 mg. 3 times daily was increased to 50 mg. 3 times daily after 3 days. A dose of 75 mg. 3 times a day was found to cause side-effects in certain cases. Improvement was related to clinical state. Thus,

of 28 patients with endogenous depression, 20 showed moderate or very marked improvement, compared with 6 out of 19 with neurotic depression. Improvement usually appeared within one or 2 weeks and was well sustained [maximum period of observation 9 months].

Side-effects occurred in 20 cases, but were usually mild, taking the form of dry mouth in 8 cases, tremor in 3, and dyspepsia in 2, with nausea, palpitations, and drowsiness in other cases. However, in 3 cases treatment had to be stopped because of severe side-effects: grand-mal attacks after 3 days in one case, disorientation after 3 days in another, and nausea and vomiting in the first week in a third patient. Grand mal possibly accounted for loss of consciousness in a fourth patient, who, however, continued to take amitriptyline at lower dosage with no further ill effect. The authors compare their results with those reported for imipramine, and conclude that amitriptyline is as effective in the treatment of endogenous depression and causes fewer side-effects.

[This study is based on uncontrolled clinical impressions in a small number of very mixed cases with a wide age range and can only be regarded as indicating trends. No statistical analysis is attempted.]

Christopher Wardle

TREATMENT

629. Place of and Indications for Thiopropazine in Psychiatric Treatment. (Place et indications de la thio-propérazine en thérapeutique psychiatrique)

P. A. LAMBERT. *Psychiatria, neurologia, neurochirurgia [Psychiat. Neurol. Neurochir. (Amst.)]* 65, 9-22, Jan.-Feb., 1962. 2 figs., 18 refs.

The author reviews the results of a 4-year study of thiopropazine ("majeptil") in the treatment of psychiatric patients in various hospitals in Lyons and elsewhere in France. During the 4-year period over 1,000 patients were given the drug, the history and place of which among other phenothiazine derivatives are described. The drug is characterized by a piperazine side-chain, its anti-emetic action, and cataleptic features. The author distinguishes this group of phenothiazines from levomepromazine, which has an aliphatic side-chain, marked sedative effects, and little cataleptic activity.

Thiopropazine was found to produce outstanding effects in schizophrenic states, both acute and chronic, above those of any other phenothiazine. Chronic hallucinatory psychosis is another indication for the drug, and the absence of production of somnolence is an additional advantage. Mania is a third indication, and the drug was sometimes combined with levomepromazine in the treatment of these patients. It was occasionally found helpful in epileptic psychosis, character disorders associated with mental retardation, senile psychosis, and confusional states. It has no place, however, in the treatment of depression or anxiety. Secondary side-effects include an akinetic state and excito-motor crises particularly affecting the mouth and tongue, but also including torticollis, opisthotonos, and hyperextension of the arms; these crises occur early in treatment. Also described are an akinetic, hypertonic state akin to encephalitic Parkinsonism and a hyperkinetic, hypertonic state with tremors; these Parkinsonian-like effects occur later in treatment, often only after many months. Autonomic changes include sweating,

suffusion of the face, increased salivation, and seborrhoea. Particularly alarming is a state of shock, with pallor, hyperthermia, and sweating.

The dosage is critical, the aim being to achieve a maximum therapeutic effect with a minimum of side-effects. Strict medical supervision is necessary, at least during the first month of treatment. Four types of treatment are described: (1) continuous progressive treatment with a dosage of up to 30 or 60 mg. per day; (2) discontinuous treatment; (3) combination of thiopropazine with a sedative neuroleptic drug, especially levomepromazine; (4) in combination with anti-Parkinsonian compounds. The last two methods are thought to be preferable. The continued use of thiopropazine in after-treatment is stressed. *J. S. Bearcroft*

630. Results of Treatment with Thiopropazine (Majepil) in 100 Patients in a Psychiatric Hospital. (Résultats du traitement à la thiopropazine (majepil) chez 100 malades dans un hôpital psychiatrique)

P. A. F. VAN DER SPEK. *Psychiatria, neurologia, neurochirurgia* [Psychiat. Neurol. Neurochir. (Amst.)] 65, 23-64, Jan.-Feb., 1962. 21 figs., bibliography

The author reviews the place of "majepil" (thiopropazine) in psychiatry, recounts its history, and describes the treatment of 103 patients, mostly with chronic illness. The drug was used as a form of chemical shock, analogous to malaria therapy in neurosyphilis. He describes the well recognized motor effects, such as akinetic and hyperkinetic states with or without hypertonus, and the motor crises, often amounting to a catatonic-like state. These occurred sometimes several days after withdrawal of the drug. The neurovegetative symptoms included sweating, seborrhoea, mild hypotension, coldness, thirst, bradycardia as well as tachycardia, drooling, insomnia, hyperpyrexia, and vomiting; sudden falling occurred in one patient and a possible sensitivity to small doses in one other. When given by injection majepil was more likely to cause a rise in temperature. The mode of treatment was the discontinuous shock method, beginning with 10 mg. of the drug orally, increasing daily up to an eventual maximum of 100 mg. per day after 5 or 6 days. The second "shock" was given only when the motor symptoms following the first had disappeared. A maintenance dose was generally employed (in most cases 3 mg. per day), and anti-Parkinsonian compounds given when required.

Psychological testing, including the Rorschach and Wechsler tests, was carried out in 14 patients and showed that under treatment the patient tended to withdraw into himself, presenting a picture of an organic state. Creativeness, as judged by the patients' paintings (some of which are reproduced), seemed to regress during treatment and for some time afterwards. Improvement in performance appeared long after cessation of treatment. This was regarded as evidence of an accumulation of majepil in the body after treatment. As to the over-all results, objective improvement occurred in 65 patients, though in some only temporarily, and of these 25 could be discharged. The most favourable response was seen in several acute psychotic patients showing manic and schizophrenic symptoms, with hallucinatory and confusional states. Little or no improvement occurred in subnormal patients, negativistic states, and hypochondriacal schizophrenic states. Motor symptoms are regarded by the author as contributing to the efficacy of the drug. He en-

countered no serious complication, but advises strict nursing supervision and temporary withdrawal of the drug when the temperature is raised. Promethazine hydrochloride ("phenergan") should always be at hand in case of untoward symptoms. *J. S. Bearcroft*

631. A Critical Appraisal of Chlordiazepoxide

F. J. AYD JR. *Journal of Neuropsychiatry* [J. Neuropsychiat.] 3, 177-180, Feb., 1962. 2 refs.

This paper from Franklin Square Hospital, Baltimore, reports the author's experience of the use of chlordiazepoxide ("librium") in the treatment of "over 200 ambulatory and hospitalized neurotics and psychotics". Anxiety was the main symptom selected for treatment with chlordiazepoxide, but in addition certain patients with obsessional symptoms were treated. The therapeutic results were assessed 2 months after treatment had been started. No controls were used. Of 200 patients given chlordiazepoxide alone to start with, 76% needed other drugs in addition within the 2-month period. In the 48 cases in which chlordiazepoxide alone was continued for 2 months the dosage varied from 30 to 300 mg. a day. The main response seen was sedation (which could be severe even after small doses). Other patients were stimulated by the drug and its effects might be like those of alcohol or amphetamine intoxication. Occasionally neurological reactions such as confusion with ataxia, dysarthria, paresis, and tremors occurred and called for immediate cessation of the treatment. Some patients had a marked increase in appetite.

The author concludes that although this drug has now been used for 2 years there is little evidence yet that it has any advantage over previously used compounds.

B. M. Davies

632. The Treatment of Acute Excitement in Endogenous Psychoses. (Zur Behandlung akuter Erregungszustände bei endogenen Psychosen)

R. TÖLLE. *Archiv für Psychiatrie und Nervenkrankheiten* [Arch. Psychiat. Nervenkr.] 203, 85-100, 1962. 19 refs.

The author describes the treatment given to 76 female patients with various endogenous psychoses who were admitted to hospital in a state of acute excitement. It was found that convulsion therapy (electronarcosis or leptazol-induced convulsions) showed better results than other forms of treatment in euphoric restless schizophrenics with subnormality, and also in patients with severe depressive psychoses. Convulsion therapy seemed to be as effective as pharmacotherapy—various members of the phenothiazine group were given—in excited and stuporose patients with catatonia, including malignant catatonia, but neuroleptic drugs were superior in patients who showed marked mood changes as well as excitement—that is, those with agitated depressions or manias—and in restless hebephrenics; generally speaking the neuroleptic drugs acted more quickly and had more general therapeutic effects than convulsion therapy. A comparison of the various phenothiazines with each other showed that the piperazine derivatives were more effective in catatonic and paranoid schizophrenics, whereas "neurocil" gave better results in patients with mood changes. In some cases a combination of the two types of drugs seemed to be the treatment of choice.

[The significance of these results was not confirmed by statistical analysis.] *J. Hoenig*

Dermatology

633. Fluocinolone Acetonide, a New Topical Corticosteroid: Clinical and Pharmacologic Evaluation

M. M. CAHN and E. J. LEVY. *Journal of New Drugs [J. New Drugs]* 1, 262-267, Nov.-Dec., 1961 [received April, 1962]. 7 refs.

By chemical modification of the corticosteroid molecule a new steroid, fluocinolone acetonide, has been synthesized which possesses increased anti-inflammatory action but does not cause sodium retention or other systemic toxic effects. At the Hospital of the University of Pennsylvania, Philadelphia, 4 mg. of fluocinolone acetonide was given daily for 3 months to 10 healthy males. Thorough clinical examinations and laboratory tests were carried out and at the end of the 90-day test no significant sequelae were observed.

A double-blind trial of fluocinolone acetonide cream and a placebo cream showed that the former was highly efficacious in 23 out of 24 patients with atopic dermatitis or inflammatory dermatoses. In another study the anti-inflammatory potency of 0.25% cream was compared with that of 1% hydrocortisone cream. In a very high proportion of cases the cream appeared to be more effective than the hydrocortisone cream. There were no instances of primary irritation or of allergic sensitization in 200 men subjected to repeated patch tests and no untoward local reactions were observed.

G. B. Mitchell-Heggs

634. The Epidemiology of Systemic Lupus Erythematosus: Preliminary Results in New York City

M. SIEGEL, S. L. LEE, D. WIDELock, E. B. REILLY, G. J. WISE, S. B. ZINGALE, and H. T. FUERST. *Journal of Chronic Diseases [J. chron. Dis.]* 15, 131-140, Feb. [received May], 1962. 2 figs., 21 refs.

The preliminary results of a long-term epidemiological investigation of systemic lupus erythematosus (S.L.E.) are reported. In all the cases studied there were at least three of the common clinical manifestations of S.L.E., together with laboratory evidence of repeated positive reactions to the L.E.-cell test or positive pathological findings, such as "wire-loop" glomerular lesions, splenic lesions, or haematocytin bodies.

In three defined adjoining health districts of New York City for which data were available for 1951 to 1959 inclusive, there was no evidence of an increase in the incidence of S.L.E. "in recent years. However, there was evidence of an increase in prevalence which was attributed to better recognition of the disease and improved medical care." The disease occurred more often in females than in males and more often in negroes than in white subjects. It was commonest among negro women between the ages of 15 and 54 years.

Serological and physical tests were carried out in relatives, and the results compared with those obtained in relatives of patients with non-collagen disease. The differences were less marked than had been expected, but the most specific abnormality associated with familial S.L.E. was the frequent occurrence of antinuclear antibodies and of chronic false positive reactions for syphilis.

E. H. Johnson

635. Amodiaquine Hydrochloride in the Treatment of Chronic Discoid Lupus Erythematosus

A. MAGUIRE. *Lancet [Lancet]* 1, 665-667, March 31, 1962. 9 refs.

From Guy's Hospital, London, the author describes the treatment with amodiaquine hydrochloride ("camoquin") of 17 patients (8 males and 9 females) with chronic discoid lupus erythematosus which had lasted from 18 months to 45 years; all had previously received at least one anti-malarial drug with other forms of therapy in addition. Six patients showed an "excellent" response with healing of all affected areas, and 6 a "very satisfactory" response with only small areas remaining difficult to control. Of the other 5 patients, there was a varying degree of improvement in 4, and one case was inconclusive as the patient discontinued treatment. All the patients are said to have responded better to amodiaquine than they had previously done to other antimalarial drugs.

The time taken to control the disease varied from 3 weeks to 6 months. Toxic effects included abdominal pain, malaise, lethargy, blue-grey pigmentation of the finger-nail beds and hard palate (the one patient so affected also developed subepithelial corneal deposits after receiving 400 mg. daily for 9 months), and pigmentation of the skin. One patient had had severe leucopenia when the drug was given earlier, but no trouble was experienced on this occasion when it was combined with corticosteroids.

It is considered that 200 mg. of amodiaquine daily is usually adequate, although 300 mg. may be given daily in resistant cases, but higher doses are unnecessary. Once the condition is controlled, only 200 mg. 3 or 4 times a week may be required.

R. R. Willcox

636. Amodiaquine Hydrochloride: Corneal Deposits and Pigmented Palate and Nails after Treatment of Chronic Discoid Lupus Erythematosus

A. MAGUIRE. *Lancet [Lancet]* 1, 667, March 31, 1962. 6 refs.

A case is described of a woman aged 38 with chronic discoid lupus erythematosus of 13 years' duration who was first treated with chloroquine over a period of 6 months, without improvement and was then given amodiaquine hydrochloride, 200 mg. twice daily. After 3 months' treatment the lesions were less erythematous; after 10 months the patient's face had returned to normal and the dosage was reduced to 200 mg. daily. After 11½ months, however, the patient complained of visual difficulties, in particular sudden flashes of light which lasted several seconds, and grey-blue subepithelial deposits considered to be due to the drug were noted.

The drug was then withdrawn, and 3 months later the corneal deposits were seen to be disappearing, but by this time a circular patch 1 inch (2.5 cm.) in diameter on the hard palate and greyish-green pigmentation of the nail beds of the 3rd and 4th fingers of each hand were observed. The abnormal pigmentation had all disappeared 9 months from the cessation of therapy.

R. R. Willcox

Paediatrics

637. Dye-binding Capacity of Serum Albumin in Hemolytic Disease of the Newborn

W. J. WATERS and E. G. PORTER. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 102, 807-814, Dec., 1961. 4 figs., 15 refs.

This study, reported from Syracuse Memorial Hospital, New York, was designed to determine the dye-binding capacity of cord serum from healthy infants and from infants with haemolytic disease, the effect of exchange transfusion on the dye-binding capacity, and whether a reduction in dye-binding capacity could be related to an increase in the concentration of bilirubin in the serum.

Cord blood was obtained from 45 healthy infants and from 27 infants with haemolytic disease due to Rh incompatibility who gave a positive reaction to the Coombs test. Ninety specimens were taken at the beginning and end of exchange transfusion from 37 infants, including 34 with Rh incompatibility and 3 with ABO incompatibility. The binding of phenolsulphonphthalein by serum albumin was measured by a modification of the method of Huggins *et al.* (*Cancer Res.*, 1949, 9, 753). The serum albumin value was estimated by the biuret method and the serum bilirubin concentration by a modification of the technique of Malloy and Evelyn.

The dye-binding capacity of serum was expressed as μg . of phenolsulphonphthalein bound per ml. of serum. In 45 healthy infants the mean value was 67.5 (range 57 to 80) and in 24 haemolytic infants the mean was 50.5 (range 20 to 67). In general it was apparent that the more severe the disease the lower was the dye-binding capacity. An increase in dye-binding capacity was found after exchange transfusion. In half of the cases the serum albumin concentration was slightly lower at the end of transfusion than at the beginning. This may have been due in part to the reduced albumin content of the donor blood. The greatest increase in dye-binding capacity was found in the serum from an infant who had received donor blood enriched by the addition of extra human albumin. An inverse relationship was noted between total serum bilirubin concentration and dye-binding capacity. There was, however, considerable variation between the amount of phenolsulphonphthalein bound by different samples of serum with the same bilirubin content.

The authors state that measurement of the dye-binding capacity may be of value when the concentration of serum bilirubin approaches levels usually considered critical (20 mg. per 100 ml. or more). Infants with a relatively high level of serum albumin and high dye-binding capacity may be able to tolerate a concentration of serum bilirubin which would be toxic if the albumin level and dye-binding capacity were lower.

G. Clayton

638. Risks Associated with Exchange Transfusion

W. J. JABLONSKI. *New England Journal of Medicine* [New Engl. J. Med.] 266, 155-160, Jan. 25, 1962. 3 figs., 26 refs.

The author, concerned with the risks of exchange blood transfusion in newborn infants, has compared, at St. Margaret's Hospital, Dorchester, Massachusetts, the mortality

and the incidence of neurological damage in such infants with those in babies not so treated. At this hospital, where there are approximately 5,000 deliveries each year, during the 7-year period 1954-60 a total of 558 exchange transfusions were carried out, 295 for haemolytic disease and 263 for hyperbilirubinaemia. The gross mortality was 4.7% for babies dying during exchange transfusion or up to 6 hours after it. Of the 263 babies transfused because of hyperbilirubinaemia 6 (2.3%) died, but probably only 4 of these (1.5%) did so as a direct result of the transfusion. During the period under review there were no proven cases of kernicterus, and there was no greater incidence of neurological defect in the 19 babies with serum bilirubin levels between 20 and 25 mg. per 100 ml. than in the 58 whose levels did not exceed 15 to 20 mg. per 100 ml. [It is difficult to understand from this paper why so many of these babies needed an exchange transfusion. An inquiry for purposes of comparison made at five other Boston hospitals showed that for these five the mean serum bilirubin level was 14.5 mg. per 100 ml., while at the author's own hospital the mean value was 16 mg. per 100 ml.; it seems that he may have been misled into thinking that these babies were at special risk.]

In discussing causes the author refers to reports by other workers regarding hypoxia, the giving of sulfisoxazole (sulphafurazole), and sepsis as causing high levels of bilirubinaemia, but claims that none of these factors could be incriminated in his cases. He concludes that in uncomplicated cases of hyperbilirubinaemia in full-term babies and the larger premature infants there is no indication for exchange transfusion until the serum bilirubin level reaches 25 mg. per 100 ml. [In referring to neurological defect the author gives no criteria for such lesions, nor does he state what examinations were carried out—for example, whether hearing was fully tested and if so whether in one or both ears. The results reported may well apply only to cases managed in this particular hospital.] A. White Franklin

639. A Rare Form of Epigastrius Parasiticus in Conjunction with Other Malformations. (Редкая форма Epigastrius parasiticus в сочетании с другими пороками развития)

V. V. GAVRILUŠOV. *Вопросы Охраны Материнства и Детства* [Vop. Okhrany Materin. Dets.] 7, 86-87, March, 1962. 2 figs.

Epigastrius parasiticus is one of the very rare forms of asymmetrical united twins in which a part of one twin is united to the other in the region of the epigastrium. In 1935 Ternovsky described 22 cases of this type. The present case was admitted to hospital 2 hours after delivery. In the epigastric area of the formed twin, which weighed 3,500 g., there was a fully formed additional lower extremity with a malformed scrotum and a penis, while in the anal region of the "parasite" there was a wart-like formation. This lower extremity was firmly united with the soft tissues of the epigastric region and the right ribs, and radiography revealed that it contained bone formation and an embryonic pubic bone. There was also an umbilical hernia measuring

6×6×5 cm. covered by a membrane, the defect in the anterior abdominal wall measuring 5×5 cm.; the hernia could be easily reduced. There was also a bilateral talipes and a congenital heart defect.

An operation was performed 12 hours after admission after a course of intramuscular injections of penicillin and streptomycin (50,000 units twice a day) and intravenous injections of glucose and physiological saline solution. The embryonic hernia of the umbilicus was dealt with extra-peritoneally. The fully formed twin recovered.

H. W. Swann

640. **Psychologic Correlates of Premature Birth: a Review** G. WIENER. *Journal of Nervous and Mental Disease* [J. nerv. ment. Dis.] 134, 129-144, Feb. [received May], 1962. 42 refs.

CLINICAL PAEDIATRICS

641. **The Choreiform Syndrome in Children** H. F. R. PRECHTL and C. J. STEMMER. *Developmental Medicine and Child Neurology* [Develop. Med. Child Neurol.] 4, 119-127, April, 1962. 5 figs., 19 refs.

While taking EEG's [electroencephalograms] on some hyperactive children who had been referred to the doctor because of poor school performance, the authors noticed that there were chorea-like twitchings of the limbs and head, showing up on the EEG as muscle artefacts from the cervical and temporal muscles. A group of 50 children were therefore investigated very fully. These children showed choreiform movements, by which we mean slight, jerky movements occurring quite irregularly and arrhythmically in different muscles. The muscles of the tongue, face, neck and trunk were involved in all cases, but in a small group (18%) the distal muscles were not involved and these cases were grouped together as the "proximal form". The question whether there was a causal relationship between these neurological phenomena and the behavioural problems for which the children were referred is discussed. The case-histories showed that 66% of the patients had had one or more obstetrical or postnatal troubles. In another 12% the histories suggested that complications had probably occurred, though detailed information was lacking.

Finally, the authors refer to the work by Dijkstra on the hyperexcitability syndrome which he described in the neonatal period and which, on follow-up, was significantly related to the choreiform syndrome later. The choreiform syndrome seems to be a form of minimal brain damage and falls, by definition, into the category of cerebral palsy. No successful form of drug therapy has yet been discovered. [Authors' summary.]

642. **Infection following Splenectomy in Childhood** A. G. R. LOWDON, J. H. WALKER, and W. WALKER. *Lancet* [Lancet] 1, 499-504, March 10, 1962. 33 refs.

Removal of the spleen carries certain operative risks and some danger of postoperative thrombosis, but there have recently been suggestions that splenectomy in children may be followed by increased susceptibility to infection. The authors have reviewed all the 75 children subjected to splenectomy at the Royal Victoria Infirmary and the General Hospital, Newcastle upon Tyne, between 1943 and 1960.

Of the 75 children severe infection later developed in 4. A girl with hereditary spherocytosis underwent splenectomy at the age of 4 months; at the age of 11 months she was admitted to hospital with pneumococcal meningitis, from which she recovered. A boy with thrombocytopenic purpura who was subjected to splenectomy at the age of 20 months died from pyaemia 3 weeks after operation. Splenectomy was carried out in a boy of 10 years with thrombocytopenic purpura; 3 months after operation he had fulminating pneumococcal meningitis from which he recovered, only to die 2 years later from pneumococcal septicaemia with adrenal haemorrhage. A boy with thrombocytopenic purpura and haemolytic anaemia had undergone splenectomy at the age of 4 years; 16 months after operation he had pneumococcal meningitis and over the next 5 years suffered 11 further infections including fulminating attacks of pneumonia and meningitis.

After reviewing the relevant literature, the authors conclude that in a few cases splenectomy does predispose to infection, which usually supervenes within 2 years of operation, and that the risk is greatest if the operation is carried out in infancy.

[It might have been interesting to study a control series of children after some other form of abdominal surgery such as appendectomy or relief of intussusception.]

P. C. Reynell

643. **Intermittent Peritoneal Dialysis in the Management of Acute Renal Failure in Children**

J. N. ETTELDORF, W. T. DOBBINS, M. J. SWEENEY, J. D. SMITH, G. L. WHITTINGTON, J. A. SHEFFIELD, and R. W. MEADOWS. *Journal of Pediatrics* [J. Pediat.] 60, 327-339, March, 1962. 28 refs.

At the F. T. Tobey Memorial Children's Hospital, Memphis, Tennessee, 5 children between the ages of 3 months and 11 years with acute renal failure were subjected to intermittent peritoneal dialysis for periods ranging from 5 hours to 33 days. The indications for dialysis included the presence of one or more of the following: oliguria, anuria, oedema, hyperkalaemia, azotaemia, hypervolaemia, cardiac failure, encephalopathy, and drug intoxication. In one case the procedure was repeated 85 times during a 33-day period; the patient developed peritonitis after 22 days of dialysis, but responded quickly to treatment.

The dialysis fluid consisted of either Grollman's solution with or without potassium, depending on the serum potassium level, or lactated Ringer's solution. The use of hypotonic solutions was avoided, even in the presence of hypertonic dehydration, because of the possibility that rapid shifts of fluid across the peritoneal membrane might produce acute hypervolaemia. In one critically ill child this precaution was inadvertently not taken, with a fatal result. The dialysing fluids were introduced by gravity through a closed system, and the fluid was allowed to equilibrate for 60 to 120 minutes. The electrolyte composition and osmolality of the dialysis fluid were varied to meet the needs at any given time. Small losses of plasma protein in the peritoneal washings occurred; [there remains a need for a study of the diffusion of plasma proteins across the peritoneal membrane in order to determine the advisability of adding serum albumin to the dialysing fluids].

The authors recommend that intermittent peritoneal dialysis in renal failure should be reserved for potentially reversible cases.

Marianna Clark

Medical Genetics

644. Sex-chromosome Abnormalities in a Population of Mentally Defective Children

J. L. HAMERTON, G. M. JAGIELLO, and B. H. KIRMAN. *British Medical Journal* [Brit. med. J.] 1, 220-223, Jan. 27, 1962. 6 figs., 23 refs.

This report from Guy's Hospital Medical School and the Fountain Hospital, London, deals with a survey of 425 mentally defective children (229 males and 196 females) in the Fountain Hospital who ranged in age from a few months to 20 years. Of these patients 89 were mongols, 169 were spastic mental defectives, and 167 were non-spastic defectives. All the mental defectives were classed as low-grade and some had somatic anomalies other than spasticity.

Smears of buccal mucosal cells from the entire population were examined for sex chromatin. This revealed one female and one male in whom the buccal smear findings were at variance with the phenotypic sex. A female with secondary amenorrhoea was found to have single sex chromatin bodies in 22% of her cells and double bodies in 10%. In this case chromosome studies on cultures of peripheral-blood leucocytes were thought to indicate a triple-X sex chromosome constitution. A male mongol was found to be chromatin-positive and chromosome studies indicated an XXY-trisomy-21 constitution. The results of chromosome studies on peripheral-blood leucocytes are also reported in a third patient, a chromatin-positive female with many of the features of Turner's syndrome. In this patient 22% of the buccal mucosal cells were chromatin-positive, and chromosome studies indicated one normal X chromosome and an isochromosome of the long arm of X. The frequency of sex chromosome abnormalities in mentally defective individuals is discussed.

[The authors do not state in how many patients with "normal" sex chromatin results, other than the third case, chromosome studies were carried out. The possibility of mosaicism in the triple-X female is not discussed.]

A. G. Balkie

645. A Review of Chromosome Studies in the Diagnosis of Mongolism: Case Report of a Chinese Infant

P. E. CONEN, A. G. BELL, and C. P. RANCE. *Journal of Pediatrics* [J. Pediat.] 60, 533-539, April, 1962. 3 figs., 12 refs.

646. The Rhesus and MN Blood Groups and Disease

J. A. BUCKWALTER and G. V. TWEED. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 479-485, Feb. 17, 1962. 7 refs.

In this prospective study the distribution of Rhesus and MN blood groups among 1,030 patients with duodenal ulcer, 348 with gastric ulcer, 170 with gastric carcinoma, 540 with rheumatic fever, and 1,153 with diabetes mellitus was compared with that in 2,186 "controls". All the patients were seen either at the University of Iowa Hospital or the Iowa City Veterans' Administration Hospital. About two-thirds of the peptic ulcer patients had undergone operation and the diagnosis was based on the operative and/or pathological findings; in the remainder it was based on x-ray and clinical

examinations. Cancers were histologically proved, and diabetes was diagnosed from the results of clinical and laboratory investigations. Operations for mitral stenosis had been performed on two-thirds of the rheumatic fever patients and the diagnosis was determined by histology; clinical and laboratory findings in the other rheumatic fever patients resulted in their inclusion. The control group consisted of physicians, students, and technicians (45%), spouses of the patients (40%), and patients with other diseases (15%). The blood-group distributions of the three components of the control group were not significantly different ($P < 0.05$). Patients and controls were of the same ethnic group, lived in the same area, and were seen during the same period. The same technician typed all blood samples, using the same standard titres and type-specific antisera.

A table shows for each disease group the absolute and percentage distributions of controls and patients by the presumptive Rhesus genotypes, which the authors denote as rr , R_1R_1 , R_1r , R_1R_2 , R_2r , R_0r , and $(r'r')r$; or respectively, cde/cde , CDe/CDe , CDe/cde , CDe/cDE , cDE/cde , cDE/cde and $\left(\frac{Cde}{cde}\right)$; in this study, because of scarcity of appropriate antiserum, genotype R_2r was included in R_2R_2 . Other tables show similar distributions for the genotypes MM, MN, and NN. The distributions in patients and controls were compared by the conventional χ^2 test, and a modification of Woolf's method (*Ann. hum. Genet.*, 1955; 19, 251) was used to compare the frequency of the disease in rr with other Rhesus groups and in MM with other groups of the MN system. Statistically significant differences were found between patients and controls in the Rhesus distributions for each disease studied except diabetes mellitus. Thus while only 13.89% of the controls were of genotype R_1R_2 , 22.06% of the duodenal and 20.69% of the gastric ulcer patients were of this genotype. The incidence of these diseases in R_1R_2 genotypes was estimated to be respectively 1.86 and 1.64 times as great as in the rr genotype. Again the proportion of patients with gastric carcinoma who were of type R_1R_1 and R_2r was 12.35% and 7.65% respectively, compared with 17.51% and 14.63% in the controls. The incidence of this disease in R_1R_1 and R_2r genotypes was estimated at 0.56 and 0.42 times that in rr genotypes; there is some evidence, not confirmed by Woolf's method, of an excess of gastric carcinoma in R_1R_2 genotypes compared with controls. The proportion of rheumatic fever patients with the rare genotype $(r'r')r$ was 2.79% and greater than that in controls (1.15%).

Only one statistically significant difference between patients and controls was found in the MN distributions; these showed that 23.70% of the rheumatic fever patients were of genotype NN, in contrast to 17.89% of the controls. It was 1.50 times greater than in genotype MM.

E. A. Cheeseman

647. Recent Advances in the Chemistry of Inheritance

S. S. COHEN. *Journal of Pediatrics* [J. Pediat.] 60, 586-600, April, 1962. 5 figs., 40 refs.

Public Health

648. **Some Aspects of the Geographical Distribution of Hereditary Diseases of Man.** (Некоторые аспекты географического распространения наследственных болезней человека) N. P. SOKOLOV. *Советская Медицина [Sovetsk. Med.]* 25, 3-8, March, 1962. 32 refs.

This is a general survey of the work of many Soviet and foreign scientists who have studied the distribution of several hereditary diseases in various parts of the world. The author points out that the proportion of subjects with any one disease to the general population varies considerably in different regions, and that this is often associated with a relatively high or low content of certain minerals in the soil, or in other cases with isolation of the people due to geographical, political, religious, or social barriers, and so leading to inbreeding and the perpetuation of recessive characteristics.

As an example of the first situation he quotes the Ankovan district of Armenia, where the content of molybdenum in the soil is high. This element causes increased activity of the enzyme xanthine-oxidase, leading to an increased concentration of uric acid in the blood; in this district 31% of the adult population suffer from gout. He also refers to the well-known prevalence of endemic goitre in Switzerland, where there is a deficient iodine content in the drinking water. In the Marshall Islands, the frequency of amyotrophic lateral sclerosis is 80 times that in Europe or the U.S.A. Again, the over-all incidence of juvenile amaurotic idiocy averages not more than one case per million; yet in one small island off the coast of Denmark with a population of 1,600 there are 23 cases of this disorder. He again quotes Switzerland as having a disproportionately large number of cases of recessive deaf-mutism, Huntington's chorea, and porphyria. He points out that morbid statistics of the distribution of hereditary disease must be studied in conjunction with an exhaustive investigation of geographical and mineralogical data (especially with regard to the soil and water content of micro-elements), as well as social causes of isolation which may lead to concentrated areas of inbreeding. He concludes that more information is needed about the influence of environment on the development of mutations and hereditary tendencies to disease.

L. Firman-Edwards

649. **An Attempt to Evaluate the Risk of Infection of Very Young Children (0 to 4 Years) Brought up in a Tuberculous Environment, with Reference to a Study of the Family Files of a Number of Out-patient Clinics in Paris.** (Essai d'évaluation du risque de contamination des tout jeunes enfants (0 à 4 ans) élevés en milieu tuberculisé, d'après l'étude des dossiers familiaux de plusieurs dispensaires de la région parisienne)

E. BERNARD, J. CROS-DECAM, and S. PRETET. *Annales de pédiatrie [Ann. Pédiat.]* 38, 393-399, Feb. 2, 1962.

From the Clinique de Pneumo-Phthisiologie of the Seine the authors report an investigation into the proportion of children aged 0 to 4 years who, having been brought up in a

tuberculous environment, developed tuberculosis, the purpose of the study being to ascertain to what extent the degree of infection had been influenced by modern methods of prophylaxis and treatment.

A review of 667 dossiers of cases seen at 9 dispensaries in the Paris region—children who had received B.C.G. vaccination before contact and those with tuberculosis infection of unknown or uncertain source being omitted—showed that among these 667 children, belonging to 459 families, 237 cases of direct tuberculous infection were recorded, an incidence of 35.5%. The clinical condition of the index cases, the influence of the duration and intimacy of the contact, and the habits and hygienic conditions in the household are discussed in considerable detail. It emerged that the father was the source of the infection in 50% of the cases, the mother in 30%, and a neighbour or a permanent lodger in 20%. The risk of granting patients leave of absence from a sanatorium to a home where there are children not protected by B.C.G. vaccination is emphasized. Equally dangerous, in the authors' view, is the domiciliary treatment of the adult patient in an ill-regulated household, where family indiscipline is a major factor in these infections. The evidence revealed by this inquiry leads the authors to deplore that B.C.G. vaccination is not given to all children at an early age, and they make the interesting historical comparison with a similar study carried out 30 years ago by Léon Bernard, who reported an incidence of 37.5%—that is, little higher than that in the present study.

Norman F. Smith

650. **Smallpox in Bradford, 1962**

J. DOUGLAS and W. EDGAR. *British Medical Journal [Brit. med. J.]* 1, 612-614, March 3, 1962. 1 fig.

This is a preliminary report on the outbreak of severe Asiatic smallpox which began in Bradford in January, 1962. The series included the original case, that of a Pakistani girl of 9, in whom the disease was undiagnosed at the time of death, 10 secondary cases infected in the hospital in which she died, and 3 "third-generation" cases which were also infected in the same hospital. Of these 14 patients, 6 died from smallpox and one from other causes. In the group of 10 secondary cases at least 7 patients became ill after the short incubation period of 9 days (normal 12 days), and at least 2 had the haemorrhagic type of smallpox, dying 6 and 7 days respectively after the onset of symptoms and without a focal eruption. These cases provide clear evidence of the extreme virulence of the infection. The patients with haemorrhagic smallpox had not been vaccinated; the original patient had been vaccinated in infancy [presence of a scar not mentioned] and recent re-vaccination had been unsuccessful. In none of the other secondary cases was there any evidence of previous successful vaccination.

When the secondary cases appeared nearly 900 contacts were vaccinated and kept under surveillance. For the public generally mass vaccination was not recommended, but clinics were opened and other arrangements made to vaccinate those who had some recent contact with the hospitals and patients concerned as well as others who felt that they were in-

sufficiently protected. Some 250,000 people in the city were thus vaccinated within a few weeks, and no doubt this constituted a material barrier to further spread of the infection and cut short the duration of the outbreak to about a month. The authors state that many interesting aspects of the outbreak, such as complications of vaccination and the effect of vaccination on expectant mothers and on patients receiving steroids, will be the subject of a further report.

H. Stanley Banks

651. An Epidemic of Infectious Hepatitis in a Rural Village Attributable to Widespread Contamination of Wells

K. R. WILCOX JR., F. M. DAVENPORT, D. COOHON, N. PAPSDORF, and L. D. JOHNSON. *American Journal of Hygiene* [Amer. J. Hyg.] 74, 249-258, Nov., 1961. 4 figs., 10 refs.

An outbreak of infective hepatitis occurred in a village and its surrounding districts in northern Michigan between March and August, 1959. A total of 90 cases occurred in a population of 414, the incidence being highest in the age group 5 to 14 years, in which there were 51 cases. No cases had been observed in the village in the preceding 3 years, and although cases of hepatitis were reported from adjacent areas during the autumn of the year before the outbreak and in the year afterwards, there was no evidence of an epidemic as sharp as that in the village. Water was thought to be the vehicle of infection. Although there was no common piped water supply, most of the householders had individual wells bored into the same water-bearing limestone. Many of the wells showed structural defects and coliform bacilli were detected in water samples from 36 out of 69 wells. It seemed likely that the wells and the water table had become contaminated with surface water after the spring thaw and heavy rains. The introduction of the disease into the community a few weeks previously together with the accumulation of susceptible subjects consequent upon the absence of infective hepatitis for several years past was thought to account for the intensity of the outbreak.

J. E. M. Whitehead

652. Diphtheria Immunization: an Unexpected Primary Stimulus from Schick-testing

G. BOUSFIELD and L. B. HOLT. *Monthly Bulletin of the Ministry of Health and the Public Health Laboratory Service* [Mth. Bull. Minist. Hlth Lab. Serv.] 21, 31-36, Feb., 1962. 4 refs.

In regard to immunization against diphtheria, recent events have cast doubt on the long-accepted belief that the dose of toxin *cum* toxoid used in the Schick test (1/50 MLD or 1/1,000 Lf) was far too minute to function in any way as a primary stimulus. This paper from the Wright-Fleming Institute, St. Mary's Hospital, London, reports an investigation undertaken to determine to what extent a primary Schick test could be shown to influence the response to a first injection of diphtheria antigen in the human infant. It was carried out on three groups of children aged 5 to 18 months, matched for age, of which Group A received 0.25 ml. of diphtheria-tetanus-pertussis (D.T.P.) vaccine only and were Schick-tested one month later; Group B received a primary Schick dose followed one week later by 0.25 ml. of D.T.P. vaccine and were Schick-tested again one month later; while Group C received the same primary Schick dose as Group B, but an interval of one month was allowed between the test and the dose of D.T.P., and the Schick test was repeated one month after inoculation.

It was found that a Schick-test dose of toxin certainly did "something to prime the immunological mechanism". However, of more practical importance was the fact that with the modern powerful triple prophylactics the primary Schick stimulus was of no consequence, since the reaction rates were the same in those who had and those who had not been Schick-tested. Investigations in guinea-pigs revealed only a trend in support of these findings; it is concluded that the behaviour of antigens in human beings cannot always be determined by animal tests.

John Fry

653. Incidence and Mortality Rates for Leukemia and Lymphoma

J. C. BAILAR III, M. S. HONEYMAN, and H. EISENBERG. *Public Health Reports* [Publ. Hlth Rep. (Wash.)] 77, 281-286, April, 1962. 4 refs.

The number of residents in Connecticut, U.S.A., registered at the Connecticut Tumor Registry as having leukaemia was 293 in the period 1939-41 and 618 in the period 1949-51. The most recent information obtainable showed that 6 in 1939-41 and 7 in 1949-51 were incorrectly registered and that 286 of those registered in the first period and 588 of those registered in the second period had died. The causes to which these deaths were attributed in the order of the two periods were: leukaemia 232 and 422, lymphoma 21 and 83, other diseases with leukaemia mentioned on the certificate 16 and 38 (of which 5 and 3 were "coded" as cancer), other diseases with lymphoma mentioned on the certificate 6 and 12 (of which 2 and one were coded as cancer), other diseases without mention of leukaemia or lymphoma 10 and 32 (of which 2 and 9 were coded as cancer), and unknown diseases one in each period.

The number registered as having lymphoma was 242 in 1939-41 and 500 in 1949-51. The latest information showed that 10 in the former period and 4 in the latter were incorrectly registered and that 221 and 428 respectively had died. The tabulated causes of death in the two periods were: lymphoma 157 and 331, leukaemia 16 and 15, other diseases with lymphoma mentioned on the certificate 22 and 34 (of which 19 and 15 were coded as cancer), other diseases with leukaemia mentioned on the death certificate nil and 2 (of which one was coded as cancer), other diseases without mention of lymphoma or leukaemia 24 and 44 (of which 17 and 32 were coded as cancer).

Details of the certified causes of death are given in footnotes to the table and are discussed in the text, but the main purpose of the analysis was to demonstrate that "the use of mortality data as a substitute for incidence data, or the reverse, can lead to significant errors in estimating the hazards to health associated with the various forms of leukaemia and lymphoma". By calculating ratios of incidence to mortality for these data using various methods of allocating deaths to causes and by reference to studies in ten urban areas in 1947-8 and in Iowa in 1950, the authors concluded that incidence rates were usually higher than mortality rates—for example, the published data for Connecticut in 1951 gave incidence:mortality ratios of 1.47:1 for leukaemia and 1.01:1 for lymphoma. They state that the differences appear to be due to errors both in certification of cause of death and in registration, to the inclusion of diseases other than leukaemia and lymphoma, and to differences in diagnostic criteria used for morbidity and mortality data.

E. A. Cheeseman

Industrial Medicine

654. Manual Labour and Chronic Bronchitis

P. R. DAVIS and J. M. JACKSON. *Medical Officer [Med. Offr.]* 107, 81-83, Feb. 9, 1962. 2 figs., 15 refs.

The authors develop a hypothesis concerning the effect of the acute rise of pressure (snatch pressure) which occurs within the abdomen when a man stoops and starts to lift a heavy weight. Evidence is presented from intrathoracic pressure measurements and changes in thoracic diameter that this pressure is transmitted to the thorax and there is a rapid increase in pressure associated with a sudden increase in lateral chest diameter. It is postulated that these sudden changes in pressure may damage the lung and result in "chronic bronchitis". In the docks at Hull one dock is concerned largely with the handling of timber, whereas the other three handle general cargo. The authors state that timber dockers lift and carry in the erect position, whereas general dockers habitually stoop to lift their burdens. It is therefore postulated that the general dockers have more frequent changes of pressure within their thorax in the course of their work and this might lead to a higher incidence of bronchitis. In fact the rate of sickness absence due to bronchitis was found to be significantly greater in the general dockers than in the timber dockers. The authors state that there is no other difference between these two groups of men, such as smoking habits or exposure to air pollution, that could account for these differences.

[It is difficult to see how intrathoracic pressure changes could result in a greater liability to bronchial hypersecretion and infection, which are the main features of the syndrome of chronic bronchitis. The authors presumably postulate that emphysema might be caused, but they produce no evidence on this, nor do they give any data to support their contention that there are no other differences between the groups of workers that might account for their difference in bronchitis absence rates.]

C. M. Fletcher

655. Contribution to the Problem of Carbon Disulphide Poisoning. A Neuro-psychiatric Clinical Study. (Contribution à la question du sulfocarbonisme. Étude clinique neuro-psychiatrique)

A. SZOBOR. *Psychiatria et neurologia [Psychiat. et Neurol. (Basel)]* 143, 178-196, 1962. 45 refs.

This study, reported from the University Psychiatric Clinic, Budapest, is based on the examination of 127 patients, all workers engaged in industrial processes employing carbon disulphide (CS_2), who suffered from intoxication with this substance. The literature on carbon disulphide poisoning is briefly reviewed. These patients, whose ages ranged from 15 to over 50 years, had been exposed to the chemical for periods varying from a few months to over 10 years. Their chief complaints were of headache (42% of cases), gastro-intestinal disturbances (31%), weakness and sensory disturbances of the limbs (24%), visual disturbances (11%), disturbances of the vegetative nervous system (31%), and disorders of memory and concentration (22%). Physical findings included vascular hypertension in 22%, cranial nerve lesions in about 80%, motor, sensory, and reflex

abnormalities in 50%, incoordination and tremors 55%, Parkinsonism 4%, and psychiatric abnormalities about 55%.

The author summarizes these findings and those reported in the literature into six clinical syndromes: (1) encephalopathy due to vascular lesions; (2) the Parkinsonian syndrome; (3) toxic polyneuropathy; (4) optic nerve lesions; (5) autonomic disturbances; and (6) psychiatric abnormalities. He concludes that the recent appearance of vegetative nervous disorders and mental changes in persons exposed to carbon disulphide should suggest the possibility of early intoxication with this substance.

J. B. Stanton

656. Byssinosis in the Cotton Industry of Egypt

M. A. EL BATAWI. *British Journal of Industrial Medicine [Brit. J. Industr. Med.]* 19, 126-130, April, 1962. 7 refs.

The incidence of byssinosis among workers in three processes in the cotton industry in Egypt has been studied at the High Institute of Public Health, Alexandria, the processes being ginning (separating cotton seeds from the lint and freeing cotton from impurities), pressing, and carding. Every third man on the pay list of the male personnel at 7 ginneries in the north of the country and at 4 in the south was examined, the men being distributed in different departments with variable degrees of exposure. Altogether 323 men were examined; female workers in ginning were excluded because they were found to be extremely unstable in holding their jobs. The findings in this group were compared with those in 203 workers in two card rooms in a large textile plant in Alexandria, selected in a similar way, and with those in a total population of 78 in two pressing plants also in Alexandria. The average duration of employment for the workers examined was 8 years in ginning, 9 years in pressing, and 9½ years in carding.

Of the 323 workers in the ginning plants 124 (38.4%) were found to have byssinosis, compared with 41 out of 78 (52.6%) in the pressing plants and 54 out of 203 (26.6%) in the carding process. The ages of those exposed and the duration of exposure were considered in relation to the prevalence of byssinosis, and it appeared that a short duration of exposure in ginning might result in earlier manifestations of byssinosis at a relatively young age. Chronic bronchitis was diagnosed in 54 (16.7%) of the workers in ginning, 11 (14.1%) of those engaged in pressing, and in 89 (43.9%) of the workers in carding, these figures indicating, in the author's view, that there was no association between the incidence of byssinosis and that of chronic bronchitis.

Since ginning is a seasonal activity there is an interruption in the exposure of the workers, this applying to a lesser extent to the pressing process. A comparison of the findings in these two groups with those in the workers in the card rooms, where exposure is continuous, showed that men employed in the first two processes have early manifestations of byssinosis at a relatively young age, whereas a higher proportion of workers in carding have later stages of the disease. It is suggested that delay in the progress of the disease is the result of periodic interruption of exposure.

Kenneth M. A. Perry

Forensic Medicine and Toxicology

657. The Larynx

K. M. BOWDEN. *Journal of Forensic Medicine* [J. forens. Med.] 9, 10-16, Jan.-March, 1962.

A general account is given of laryngeal conditions of forensic importance. Laryngeal shock, spasm, and obstruction due both to foreign bodies and to oedema are briefly discussed, together with stenosis and fractures of the larynx; the occasional occurrence of delayed death following the latter is mentioned. Many examples of these conditions drawn from the author's own experience are given in this paper, which concludes with a note on post-mortem injury to the larynx.

Gilbert Forbes

658. A Study of Modern Methods of Grouping Dried Blood Stains

L. C. NICKOLLS and M. PEREIRA. *Medicine, Science and the Law* [Med. Sci. Law] 2, 172-179, April, 1962. 2 figs., 4 refs.

Writing from the Metropolitan Police Laboratory, New Scotland Yard, London, the authors discuss briefly the disadvantages of the classic inhibition or "subtractive" techniques for the grouping of dried blood stains and compare these with two recently published "additive" methods; namely, those of Kind and of Coombs *et al.* Both these latter methods are described and certain procedures in each are criticized. A simplified and, it is claimed, improved technique, using wetted slides, is then outlined, embodying the results of the authors' experience with these additive methods. This technique has been used to group some 400 dried blood stains in respect of A₁, A₂, B, O, M, N, and Rhesus D factors. The method is stated to give satisfactory results also with saliva and seminal stains, as well as with minute blood stains on thread. At present it is not advised for dried blood clot.

[This is an important paper and practitioners in this field are advised to read the original in full.]

Gilbert Forbes

659. Treatment of Coal-gas Poisoning with Oxygen at 2 Atmospheres Pressure

G. SMITH, I. MCALEDINGHAM, G. R. SHARP, J. N. NORMAN, and E. H. BATES. *Lancet* [Lancet] 1, 816-819, April 21, 1962. 3 figs., 17 refs.

Over a recent 12-month period 32 patients suffering from carbon monoxide (CO) intoxication were admitted directly to the Western Infirmary, Glasgow. All recovered, 10 with orthodox treatment and 22 with administration of oxygen under 2 atmospheres pressure. The direct admission was made possible by close cooperation between the hospital and the Glasgow division of the Scottish Ambulance Association. One further patient was transferred from another hospital after treatment for several hours without response. In this case oxygen under pressure removed the CO from the blood (40% on admission), but the patient did not recover consciousness and died on the third day.

The average interval between the finding of the casualty and arrival of the patient in hospital was 30 minutes. Dur-

ing the ambulance journey the patient, if conscious, was given oxygen; if not fully conscious and suffering only from CO poisoning he received an inhalation of 5% carbon dioxide in oxygen; if unconscious and apnoeic or if respiration was much depressed he was given oxygen by a Stephenson respirator.

On arrival of the patient at the hospital the carboxyhaemoglobin (COHb) content of the blood was determined by the Harrison quantitative method, a Hartridge reversion spectroscopy being used. The readings were found to be reliable within the range of 40 to 60%, but figures above and below these levels tended to be underestimated. In the pressure chamber, if ventilation was adequate, oxygen was led to the facepiece through a 2-litre bag so that ventilation could be assisted by manual compression of the bag. Treatment was continued until COHb was no longer detectable and clinical improvement was satisfactory. Consciousness was regained after treatment with oxygen under 2 atmospheres pressure for 35 to 90 minutes. At the follow-up examination no mental deterioration was found and none of the electrocardiographic changes reported to be sequelae of CO intoxication was seen.

In a discussion the authors draw attention to the observation of Haldane in 1895 that a mouse remained perfectly normal in a mixture of 2 parts of oxygen to one of carbon monoxide at a total pressure of 2 atmospheres of oxygen and one of carbon monoxide, enough oxygen being carried in physical solution in the plasma to minimize or eliminate the need for oxygen transport by haemoglobin. In 1949 Pitts and Page showed that the half-clearance time for COHb was 19.8 minutes with oxygen at 2.5 atmospheres pressure and 68.3 minutes with air at the same pressure. It is pointed out that oxygen under pressure shortens the half-clearance time for apnoeic levels of COHb, and is beneficial in cerebral depression due to overdosage of barbiturates or in states of diminished cerebral blood flow. By this technique anoxia is quickly controlled by the carriage of some 4 volumes % of oxygen dissolved in the plasma, and the effect of CO upon the heart muscle (which is not purely anoxic) is amended. The best results are obtained by the use of oxygen under 2 to 2½ atmospheres absolute pressure.

M. A. Dobbin Crawford

660. Use of Antagonists in Drug-Induced Coma

J. ADRIANI, P. DRAKE, and J. ARENS. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 752-758, March 10, 1962. 20 refs.

The use of antagonists in drug-induced coma is reviewed in this paper from the Charity Hospital (Tulane University School of Medicine), New Orleans. Although drugs of the barbiturate group are still the most frequent cause of drug-induced coma, many other hypnotics are now available and patients may ingest more than one drug. The authors recommend that the term "analeptic" be reserved exclusively for stimulants of the central nervous system used to overcome drug-induced depression. The mode of action of analeptics is unknown, but they have little influence on the destruction or elimination of depressant drugs; thus after

the administration of an analeptic the body has the additional problem of disposing of two drugs instead of one. Central stimulants may act at almost any level from the cord to the cortex, but those which act upon the medullary centres are most suitable. There are two schools of thought concerning the value of analeptics: one claims that these drugs are not only valueless but are actually harmful, and recommends supportive measures alone; the second school maintains that analeptic drugs are life-saving if used with discretion. Three types of drugs are in common use today as stimulants. (1) Those which act by competitive inhibition; they include such drugs as nalorphine and levallorphan, and because they are weak central nervous system depressants they act by displacing the strong narcotic agent from the receptors. (2) Drugs which act largely by central excitation; these appear to be true antagonists and include pentamethylene tetrazole (leptazol), nicotinic acid, picrotoxin, and bemegride. Lastly (3) those drugs which activate the chemoreceptor cells in the carotid body and thus stimulate respiration reflexly, for example, lobeline; the activity of the drugs in this group is not confined to the respiratory centre alone, and simultaneous stimulation of other medullary centres results in nausea, vomiting, salivation, and elevation of the blood pressure. Today the most commonly used analeptics are bemegride, methyl phenidate, and ethamivan.

In this study the authors compare the efficacy of the newer analeptics with that of conventional drugs and on the basis of their results rank the drugs in the following order of effectiveness: bemegride, methyl phenidate, ethamivan, picrotoxin, pentamethylene tetrazole, nikethamide, and caffeine. Over a recent 5-year period they have treated 140 patients who were comatose or semicomatose after intentional overdosage with barbiturates or other hypnotics. In those treated with analeptics consciousness was restored in 70% of cases. The best results were obtained when the drug concerned was a short-acting barbiturate. The patients most difficult to arouse or who could not be aroused had taken glutethimide or massive doses of barbiturate or other hypnotics in combination with a phenothiazine derivative. Methyl phenidate also produced arousal, but was less effective than bemegride. Moreover, nausea, vomiting, elevation of blood pressure, and post-arousal agitation occurred frequently with this drug. The authors have had insufficient experience with ethamivan to evaluate its worth. They stress that administration of analeptics is unnecessary when the drug causing coma is volatile and can be eliminated via the lungs. Likewise, antagonists have no place in the management of coma due to overdosage with central nervous system stimulants. The authors caution against the use of analeptics for the termination of short-term surgical anaesthesia induced by thiopentone or other short-acting barbiturates in order simply that the patient may be discharged immediately after the operation. They point out that clouding of sensation persists for some hours afterwards and the barbiturate still remains in the tissues.

Hypotension is observed commonly in patients with severe central nervous system depression. Severe hypotension which does not respond to vasopressor drugs may be overcome by giving an analeptic in conjunction with such drugs. The authors stress that the administration of analeptics, which should always be carried out under medical supervision and never be delegated to other hospital personnel, takes only secondary place to general supportive measures,

including the establishment of an adequate airway, artificial respiration, aspiration of gastric contents, adequate hydration and control of electrolyte levels to ensure adequate urinary output, and prevention of atelectasis and hypostatic pneumonia.

P. T. Main

661. A Clinical and Experimental Study of Bromide Intoxication, with Special Reference to Bromureides

W. H. TRETHOWAN and T. PAWLOFF. *Medical Journal of Australia* [Med. J. Aust.] 1, 229-232, Feb. 17, 1962. 2 figs., 9 refs.

In this paper from the University of Sydney the authors describe bromide intoxication in 128 patients admitted to hospital over a 4½-year period. Of these patients, 30 were males and 98 females. The initial serum bromide levels ranged from 50 to 350 mg. per 100 ml. in 125 of the patients, and were over 350 mg. per 100 ml. in the remaining 3. An acute delirious reaction occurred in 38 patients and a subacute reaction in 48 others; the remaining 42 patients had symptoms that could not be certainly or entirely attributed to the bromide intoxication. These three clinical grades of severity showed only a very approximate correlation with the height of the initial serum bromide level. Serial estimations of bromide levels were made in 53 cases, in 11 of them on 3 or more occasions. The rate of fall showed some individual variation, but the general finding was that there was an initial rapid fall, the higher the initial level the faster being the fall, followed by a more gradual decline. It is considered that the initial rapid fall together with the inevitable delay in suspecting the condition in some cases is responsible for the lack of close correlation between the severity of the clinical condition and the initial bromide level, and also for divergencies in the literature concerning the critical bromide level for the appearance of symptoms.

The source of the bromism was traced in 33 instances to self-medication with "relaxa tabs", to a combination of these tablets with a possible bromide mixture in another 7, and to other proprietary bromureide preparations in 12; bromide mixtures prescribed by doctors accounted for 27 cases and such mixtures prescribed by pharmacists for 5. In the remaining 44 cases the source could not be accurately determined.

Experiments were carried out on the serum bromide levels occurring after the ingestion of proprietary bromureide preparations. "Sedexin", a preparation identical to relaxa tabs and containing 3 grains (0.2 g.) of carbromal and 2 grains (0.13 g.) of bromvaletone in each tablet, was given to 5 female subjects in a dosage of 6 or 8 tablets daily, while 5 other female subjects received potassium bromide, 30 or 40 grains (2 or 2.6 g.) daily. Each sedexin tablet contained the equivalent of 144.7 mg. of sodium bromide. It was found that the ratio of the daily intake of bromide per kg. body weight to the mean daily rise in serum bromide level was the same in the subjects taking sedexin as in those taking potassium bromide. In another experiment it was found that with 6 to 8 tablets of sedexin daily the average daily rise in serum bromide level ranged from 2.8 to 3.7 mg. per 100 ml.

The authors conclude that bromides no longer deserve a place in the pharmacopoeia and that the sale to the public of preparations containing bromide should be controlled.

[The formula of the relaxa tabs now on sale in Great Britain has been changed, and no longer contains any bromureide.]

J. J. Segall

Anaesthetics

662. Oral Premedication of Children with Chloral Hydrate and Scopolamine

B. ROOF. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 194-200, March-April, 1962.

Choice of premedication for children is a complex matter, for premedication influences not only the psychic aspects of anesthesia induction, but also safety during anesthesia induction and maintenance, and safety and comfort during the recovery period.

Chloral hydrate-scopolamine solution was administered to 127 children and produced a satisfactory hypnotic response in comparison to other drug combinations studied. Safety during all phases of anesthesia care did not appear to be reduced. Although the drying effect was not optimum, it was clinically satisfactory. This could probably be improved either by increasing the dose of scopolamine, or by substituting 1-hyoscyamine, which has been found effective in a dose of 0.0125 mg. per pound [0.0275 mg. per kg.]. While not especially pleasant-tasting, it was almost invariably acceptable to children between ages 1 and 13.

Since evidences of overdosage, such as respiratory depression during anesthesia, were rarely and questionably evident, and since prolongation of effect was also rare, it appears reasonable in the future to use larger doses to see if the hypnotic effect can be further increased without compromising safety.—[Author's summary.]

663. Investigation of the Usefulness of Trimethobenzamide ("Tigan") for the Prevention of Postoperative Nausea and Vomiting

B. WOLFSON, M. TORRES-KAY, and F. F. FOLDES. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 172-177, March-April, 1962. 8 refs.

A trial of the efficacy of trimethobenzamide in the prevention of postoperative nausea and vomiting is reported from the University of Pittsburgh School of Medicine, Pennsylvania. The drug was given by intramuscular injection to 383 patients after operation, while 487 received a placebo. Of the patients in the trimethobenzamide-treated group 26.4% received ether anaesthesia, 56.4% general anaesthesia with other agents, and the remainder regional anaesthesia. In the control group ether was given to 30.4%, other types of general anaesthesia to 52%, and regional block to the remainder. The majority of the patients receiving ether anaesthesia were children undergoing tonsillectomy; they were given two doses of equal amount of trimethobenzamide (50 to 200 mg. depending on the child's weight), the first dose 60 to 90 minutes before operation and the second 3 hours after operation. All other patients were given 3 doses, each of 200 mg., at the end of anaesthesia and 3 and 6 hours after operation respectively. Placebo injections were given at the same timings.

It was found that trimethobenzamide offered no protection against postoperative nausea and vomiting after ether anaesthesia and only moderate protection after the other forms of anaesthesia. However, the drug was useful when administered intramuscularly with the premedication to pre-

vent nausea and vomiting during induction and maintenance of ether anaesthesia in children and when administered intravenously for the treatment of postoperative nausea and vomiting.

Mark Swerdlow

664. Haloperidol ("Serenase") in the Prevention of Postoperative Nausea and Vomiting. [In English]

V. DYRBERG. *Acta anaesthesiologica Scandinavica* [Acta anaesth. scand.] 6, 37-47, 1962. 18 refs.

The prophylactic use of haloperidol reduced postoperative nausea from 28.6% to 7.6% in males and from 49.5% to 20.3% in females during the first 6 postoperative hours. Vomiting was reduced from 14.3% to 2.4% in males and from 32.3% to 10.8% in females. Similar results were obtained for the next 18 hours. The findings in the control groups suggest that the incidence of postoperative nausea and vomiting is independent of the age of the patient and the duration of the anaesthesia. A higher over-all incidence of postoperative nausea and vomiting was found in women than in men. Analysis of the operations performed suggested that a difference exists between the two sexes in the reaction to intraperitoneal manipulation, and that this is the factor which causes a higher incidence of postoperative vomiting in women than in men.

Haloperidol 5 mg. was found to be more active as an antiemetic than 50 mg. of chlorpromazine. It reduced the incidence of reflex movements during light anaesthesia and produced complete amnesia for the anaesthetic period, while some of the controls afterwards gave evidence of some degree of awareness during the anaesthesia. Haloperidol is recommended for the treatment of established postoperative vomiting and for prophylaxis on special indications.—[Author's summary.]

665. Prevention of Recurarization

L. WISLICKI. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 195-199, March, 1962. 24 refs.

For prevention of recurarization after gallamine it is necessary to take into account four factors which, amongst others, may promote this complication: As gallamine is wholly excreted in the urine it should not be used in renal insufficiency or in kidney surgery because under these conditions its elimination may be greatly delayed. Such prolonged retention may outlast the antagonistic effect of neostigmine. After gallamine has been given in patients with impaired renal function caution should be exercised in the postoperative use of morphine and similar narcotics because they may enhance a residual neuromuscular block sufficiently to become clinically manifest. As the likelihood of recurarization will increase with the amount of gallamine given, moderate doses are of value for certain operations when complete respiratory control is not imperative.

The two fundamentally different principles are discussed which govern at present the administration of neuromuscular blocking agents, and complications are enumerated which may be caused by each of the three relaxants now in common use.—[Author's summary.]

Radiology

RADIODIAGNOSIS

666. **The Pacchionian Granulations in the Air-encephalogram.** (Pacchionische Granulationen im Pneumencephalogramm)

G. HUBER. *Archiv für Psychiatrie und Nervenkrankheiten* [Arch. Psychiat. Nervenkr.] 203, 101-110, 1962. 5 figs., 11 refs.

In all cases admitted to the University Psychiatric Clinic, Heidelberg, between 1948 and 1957 in which air encephalography had been performed (a total of 1,296) the pneumoencephalograms were scrutinized for the appearance of entry of air into the Pacchionian bodies. (Excluded from the series were cases of intracranial tumour, endogenous psychosis, and those with technically inadequate encephalograms.) It was found that 47 cases (3.6%) showed Pacchionian granulations. These were seen most commonly in the anterior half of the cranium in the area of the frontal lobes (36 cases), while in 16 cases they appeared over the parietal lobes; thus in 5 cases they occurred in both areas. An analysis of the underlying pathological conditions in these patients did not show that the x-ray findings were in any way diagnostic; they can, in fact, appear in healthy patients, and do not seem to depend on the existence of cortical atrophy. Only 53% of the present patients had external hydrocephalus or showed signs of dementia. The largest proportion of these cases were due to various types of primary cerebral atrophy, cerebral arteriosclerosis, and head injuries. Age seemed to be a factor, as 27 of the patients were over 40, and there was a definite age gradient, in that 10 patients were in the 6th decade, 17 in the 5th, 8 in the 4th, and 3 each in the 3rd and 2nd decades of life. This is in accordance with the anatomical finding that the Pacchionian bodies increase in number and in size with advancing age. J. Hoenig

667. **Inclined Frontal Tomography in the Examination of the Mediastinum**

P. MARKOVITS and J. P. DESPREZ-CURELY. *Radiology* [Radiology] 78, 371-380, March, 1962. 9 figs., 10 refs.

The object of the technique described in this paper from the Institut Gustave-Roussy, Villejuif, France, is to dissociate the superimposed images found in the conventional chest film. Frontal tomograms obtained with a vertical sweep do not do this except in the rare very favourable case. The vertical sweep does not make allowance for the obliquity of the tracheo-bronchial tree; with the horizontal sweep the plane of the tracheo-bronchial tree must be positioned parallel with the film. The information derived from the examination is particularly helpful to the surgeon and radiotherapist in determining the type of treatment and assessing results in cases of bronchial carcinoma.

The technique is simple, but special apparatus is necessary. The tube is fixed and directed in the horizontal plane. The patient sits in a chair which rotates with the same speed and in the same direction as the film-holder. The inclination of the film-holder is variable, permitting adjustment parallel to the tracheo-bronchial axis. The particular angle of the

inclination is determined from a lateral film of the thorax. The focus-film distance varies from 2.20 to 2.60 metres. An arc of rotation of 60 degrees will give a tomographic cut about 1 mm. in thickness. Normally 5 tomograms are obtained spaced at 0.5-cm. intervals so that the middle one passes through the middle plane of the tracheo-bronchial tree. Generally one cut will present a well-defined image of the tracheo-bronchial tree from the larynx to the inferior lobar bronchi; the middle-lobe bronchi do not appear because of their antero-posterior orientation.

Of 231 cases examined with this technique, the radiological and endoscopic findings were in accord in 200. In the remaining 31 the discrepancy related to the status of the carina. The technique tends to indicate that the enlargement of this area is more pronounced than is found at bronchoscopy. John H. L. Conway-Hughes

668. **Pulmonary Embolism**

F. G. FLEISCHNER. *Clinical Radiology* [Clin. Radiol.] 13, 169-182, July, 1962. 15 figs., 12 refs.

669. **Aneurysm of the Sinus of Valsalva.** (Das Aneurysma des Sinus Valsalvae)

A. DÜX, H. H. HILGER, A. SCHAEDE, and P. THURN. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 319-341, March, 1962. 4 figs., bibliography.

In the absence of the common characteristic signs, the diagnosis of congenital aneurysm affecting the sinus of Valsalva (sinus aortae) is well-nigh impossible by the usual means. Ordinary venous angiocardiology is of little help. To obtain full information aortography or left angiocardiology is indispensable and it must be carried out in two planes and in consecutive phases. Working at the University Medical Clinic, Bonn, the authors have succeeded in diagnosing the condition four times in the living patient. They were able to discover additional facts, such as perforation of the aneurysm into the right atrium or into the pulmonary artery, the concurrent changes in the coronary arteries, as well as various other complications, and these are discussed and illustrated. F. M. Abeles

670. **The Radiological Examination of the Colon by Means of the Double-contrast Enema. The Malmö Modification.** (Über die röntgenologische Untersuchung des Dickdarmes mit der Doppelkontrastmethode. Die Malmömodifikation) S. WELIN. *Radiologe* [Radiologe] 2, 87-100, March, 1962. 24 figs., bibliography.

The modified method for radiological examination of the colon here described has now been employed at Malmö General Hospital, Sweden, for 8 years. Because of the necessity of having the colon free of all mucus and faecal matter a special room was built, equipped with 5 adjacent lavatories, 3 undressing cubicles, and 3 rest rooms. The double-contrast enemata used show a reading of 6.5 on Philips specific gravity tester (though this is not their true specific gravity); they contain tannic acid and a purging

agent, and are available commercially under the name of "cyclodrast". Atropine, 1 mg., is given as a routine to counteract griping and to prevent accidents in hypertensive patients. So far some 20,000 such examinations have been carried out and nearly 10% of the patients have been over the age of 70.

The author states that by this method even the smallest polypi can be visualized. In fact, polypi were found in 13.5% of all cases examined, a figure which corresponded exactly with that reported by the pathologists for a necropsy series. Small polyps, as such, are not significant, but they should be watched for signs of growth. The appearance of a retraction at the base indicates malignancy. In the author's experience, in about one-fifth of cases a polyp turns out to be malignant. An attempt should therefore be made to obtain a profile view of any polyp found, in order to verify the presence or absence of the significant basal retraction.

F. M. Abeles

671. **Shrinkage Deformity at the Recto-sigmoid Junction.** (Die Schrumpf-Deformität des Darmes im Grenzgebiet zwischen Rectum und Sigma)
G. THEANDER and L. WEHLIN. *Radiologe [Radiologe]* 2, 100-107, March, 1962. 14 figs., 3 refs.

In this study, reported from Malmö General Hospital, Sweden, of shrinkage deformity of the recto-sigmoid junction, the meeting point between the fixed rectum and the mobile sigmoid, the authors point out that, radiographically, indentations on the anterior wall near the sacral promontory seen in the lateral view are in most cases pathognomonic of pelvic endometriosis. Even if not caused by this condition they still are seen mostly in women, mainly as the result of post-irradiation fibrosis or due to enlargement of the female pelvic organs. Similar changes occur in peritoneal carcinomatosis.

F. M. Abeles

672. **Roentgenologic Findings in Growing Long Bones in Phenylketonuria: Preliminary Study**
S. B. FEINBERG and R. O. FISCH. *Radiology [Radiology]* 78, 394-398, March, 1962. 2 figs., 13 refs.

At least 1% of mental defectives in State institutions in the U.S.A. suffer from phenylketonuria; it occurs in either sex, the incidence being one out of 40,000 births and one out of 4 of the offspring of phenylketonuric parents. The majority of the children are blond, fair-skinned, and blue-eyed, and are mentally retarded. Treatment consists in the use of phenylalanine-deficient milk. Originally the radiological changes were directly ascribed to dietary restrictions, but the authors of this paper from the University of Minnesota, Minneapolis, do not at present consider that diet is the direct cause of the bone-growth changes, which may be related to tyrosine metabolism.

In the present study 33 patients were examined; 5 who had strongly positive radiological findings were receiving dietary treatment and 4 with less positive changes were either not given dietary treatment or were inadequately treated. In some cases spontaneous improvement occurred in spite of maintenance of dietary restrictions. The question of an unusual form of rickets was raised in the first case observed; the changes, however, occurred at the age of 3 months, earlier than would be expected in dietary rickets. Metaphyseal cupping was noted, but there was no dissolution or fraying of the metaphyseal margin as is seen in rickets.

In phenylketonuria the metaphysis does not vanish as in rickets, nor is there widening of the epiphyseal-metaphyseal space. One of the most striking features is the production of sharply circumscribed, calcified, perpendicular spicules extending from the metaphyseal side of the epiphyseal plate into the columnar and proliferating zones of cartilage. Generalized demineralization is not a normal part of the picture.

John H. L. Conway-Hughes

RADIOTHERAPY

673. **Radiation Therapy in the Treatment of Intracranial Tumors**

R. J. BLOOR, A. W. TEMPLETON, and R. S. QUICK. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine [Amer. J. Roentgenol.]* 87, 463-472, March, 1962. 16 figs., 14 refs.

A total of 83 patients completed a planned course of radiation therapy for intracranial neoplasms at the Henry Ford Hospital, Detroit, between January, 1955, and December, 1960. The tumours present did not include meningioma or tumours of the pituitary and spinal cord. Astrocytoma constituted the largest group, the numbers of Grade-III and Grade-IV tumours exceeding the numbers of Grade-I and Grade-II, the last two being treated only in cases of recurrence after surgery. The indications for treatment of intracranial metastases from primary tumours elsewhere and the value of such treatment are briefly discussed.

Because accurate location of many intracranial tumours is difficult a form of regional therapy was adopted and a simple reproducible 4-field arrangement developed. This technique was based on the use of two pairs of coaxially opposed fields at right-angles to each other in a plane parallel to a line joining the supraorbital ridge and the external auditory meatus. To irradiate tumours situated asymmetrically within the cranial cavity the central axes of the opposed fields could be displaced to one side or other of the sagittal or coronal plane, with adjustment of the dose delivered by each field if necessary to achieve the desired shape of high dose volume. Nine representative field arrangements are illustrated.

In all cases radiation was with 250 kV, having a half-value layer of 3 mm. Cu, the maximum dosage being limited to 4,000 r. in 30 to 35 days. No allowance was made for absorption in the bones of the cranial vault. The daily input was gradually increased over the first week. The results in cases of Grade-I and Grade-II astrocytoma, ungraded astrocytoma, oligodendroglioma, ependymoma, and medulloblastoma are given in terms of actual survival of the patient and also as an over-all percentage in terms of those able to work, those with some neurological deficit, and those without relief. The results in cases of Grade-III and Grade-IV astrocytoma are assessed in more detail, survival after surgery with radiotherapy and after surgery alone and the cumulative mortality curves being described. The results are also compared with those of Bouchard and Peirce (*Amer. J. Roentgenol.*, 1960, 84, 610).

From the findings the authors conclude that postoperative irradiation in cases of high-grade astrocytoma leads to a definite improvement in both quality and duration of survival. An increase in dosage to 5,000 r. in the same over-all time with this technique is discussed.

J. D. Bradshaw

674. Should we Treat Glioblastoma Multiforme? A Study of Survival in 425 Cases

J. M. TAVERAS, H. G. THOMPSON, JR., and J. L. POOL. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] **87**, 473-479, March, 1962. 7 figs., 5 refs.

The management of cases of glioblastoma is discussed with reference to 425 cases, verified at biopsy examination, seen at the Neurological Institute of the Presbyterian Hospital, New York, between 1943 and 1955. In 377 cases frank glioblastomata were present; the tumours in the remainder contained astrocytomatous elements. Of the 425 patients (257 male and 168 female), 365 (86%) were between 41 and 70 years of age. Of 114 patients seen between 1943 and 1948, 41 underwent partial resection but only 19 received radiotherapy. After 1948, surgery was attempted in 136 of 311 cases and radiotherapy in 160.

Before 1953 a tumour dose of 1,800 to 2,000 r. was given in 2 to 3½ weeks, followed within 3 months by a further 1,500 r. in 3 weeks. From 1953 onwards a single course of 41,000 r. in 4 to 5 weeks was given (frontal and frontoparietal tumours receiving 5,000 to 5,500 r. in 6 weeks and extensive growths 2,500 r. in 3 weeks).

Survival times were computed from the date of diagnosis. Of the patients in whom glioblastoma was diagnosed between 1943 and 1948, most of whom underwent simple biopsy but did not receive radiotherapy, 95% were dead within 3 months of biopsy and all were dead within 6 months. Of all the patients subjected to partial resection during the 13-year period of the study, 86% were dead in 6 months and 96% in 12 months. In 31 cases biopsy was followed by radiotherapy; half of these patients were alive at 6 months and 2 lived over 4 years. Of 148 patients subjected to partial resection followed by radiotherapy, 68% were alive at 6 months and 52% at 12 months.

When survival time was correlated with dosage of irradiation it was found that in patients receiving less than 2,000 r. the average survival time was shorter than in those given a higher dosage. No other differences were observed in the remainder. Sex and age of the patient and the tumour site did not influence survival. Of the entire series only 7 patients lived over 5 years; these received doses varying between 2,000 and 4,000 r. There were no long-term survivors among the patients given 4,000 to 5,500 r. in a single course.

The authors conclude that in patients with glioblastoma radiotherapy may prolong life and that surgical decompression is usually necessary. They advocate that as much of the tumour as possible should be removed followed by x-irradiation.

Harold Eckert

675. The Treatment of Carcinoma of the Larynx by Supravoltage Radiotherapy

R. MORRISON and T. J. DEELE. *Clinical Radiology* [Clin. Radiol.] **13**, 145-148, April, 1962. 2 figs., 6 refs.

Between 1954 and 1960 a total of 103 cases of true laryngeal carcinoma were treated by means of an 8-MeV linear accelerator and the results are analysed in this paper from the Medical Research Council Radiotherapeutic Research Unit and Hammersmith Hospital, London. All the patients received radiotherapy in the first instance, but 12 were later subjected to laryngectomy for recurrent or persistent disease. In 82 cases the tumours were glottic, in 18 supraglottic, and

in 3 subglottic. The stage-grouping of the tumours according to the TNM classification (in which T is extent of the primary growth, N the condition of regional lymph nodes, and M the presence or absence of distant metastases) is set out in detail. If the tumour was unilateral a single field was employed, but if it was bilateral two opposed fields were used. In the earlier cases the dose did not exceed 6,000 rads in 6 weeks, but later this was increased to 7,000 rads if the field did not exceed 25 sq. cm. or 6,400 rads where larger fields were necessary. These doses were not exceeded even if a confluent mucosal reaction did not at once develop. General constitutional disturbances were rarely seen. Local reaction caused temporary loss of voice and sometimes an irritable, unproductive cough.

The survival rate for the whole group was 82% at one year and 64% after 3 years, levelling off to 59% after 4 and 5 years; in fact, few patients died from the disease after the third year. The best results were obtained in patients with glottic tumours, the 3-year survival being 85% where the lesion was unilateral and the cord mobile, and 63% where the cord was still mobile but the disease was extending to the anterior commissure or the ventricle or subglottic region. The results in the earlier, lower dosage group were compared with those in the later, higher dosage group. The incidence of local recurrence was much reduced by the higher dosage, falling in patients with glottic tumours from 34% (of 32 cases treated) to 11% (of 19 cases) and in patients with supraglottic tumours from 86% (of 7 cases treated) to nil (5 cases treated).

E. Stanley Lee

676. Radiotherapy of Ewing's Sarcoma

P. W. SCANLON. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] **87**, 504-510, March, 1962. 10 refs.

The results of radiotherapy in 120 out of 165 cases of Ewing's sarcoma seen at the Mayo Clinic from 1905 to 1959 are reported. The "erythema-dose technique", in which a tumour dose of 800 to 1,400 r. (air) was given in 2 to 8 days; repeated once or sometimes twice after an interval of 2 months, was employed before 1950. This appeared to give better results than the technique adopted later of fractionated radiotherapy with a tumour dose of more than 4,000 r. (over about 4 weeks), orthovoltage and telecobalt equipment being used.

Preoperative irradiation was more successful than postoperative, although the number of patients was small. The poorer results with postoperative irradiation may have been due to the fact that in most of the patients the neoplasm was in the trunk. The author does not consider that the presence of distant metastases is necessarily a contraindication to palliative radiotherapy. He cites one patient with lung metastases who was alive and in excellent health 2½ years after treatment of the metastases. In his view there has been little or no improvement in the survival rates in Ewing's sarcoma as a result of "more aggressive radiotherapy". Treatment should in future be directed to the metastatic or systemic component of the disease. Published reports of the finding of circulating malignant cells in the blood stream are reviewed, and the possibility that the presence of these is a major factor in the prognosis in Ewing's sarcoma is considered. Recently attempts have been made to augment local radical treatment with chemotherapeutic agents or isotopes.

Peter Coy

ABSTRACTS OF WORLD MEDICINE

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Pathology

677. A Serum Flocculation Test for Diagnosis of Obstructive Jaundice

K. SHIMAOKA and D. FIRAT. *Archives of Internal Medicine* [Arch. intern. Med.] 109, 270-275, March, 1962. 7 refs.

At New York State Department of Health the authors have assessed a serum flocculation test, slightly modified from that described by Jirgl (*Klin. Wschr.*, 1957, 35, 938), for its value in the diagnosis of obstructive jaundice, a total of 127 tests being performed on 96 patients and 15 healthy controls. The reagents used in this test are those used for determination of serum mucoprotein, although it is not certain that the reacting material in the jaundiced serum is in fact a mucoprotein.

A positive reaction was obtained in 27 (87%) of 31 patients with bile duct obstruction, and a negative reaction in 48 (89%) of 54 jaundiced patients without bile duct obstruction. It is suggested that since the test discriminates relatively well between biliary obstruction and other causes of jaundice and since its mechanism appears to be unrelated to that of other tests, it should prove useful in the evaluation of difficult cases when routine tests give equivocal or contradictory results.

L. A. Elson

HAEMATOLOGY

678. The Complex Pattern of Response to Coumarin Drug Therapy. The Inadequacy of the Prothrombin Test as a Guide to Hypocoagulability

S. GOLUB, A. W. ULIN, and W. LIKOFF. *American Heart Journal* [Amer. Heart J.] 63, 591-599, May, 1962. 4 figs., 14 refs.

The authors of this paper from Hahnemann Medical College and Hospital, Philadelphia, describe the changes in the one-stage prothrombin time, the results of the thromboplastin generation test, and the levels of Factor VII and of Factor X (Stuart-Prower factor) in 6 healthy subjects after administration of a short course of dicoumarol. Similar values were studied in 2 patients receiving long-term anticoagulant therapy.

In the healthy subjects the authors observed notably uniform depression of the prothrombin time and Factor-VII concentration; the concentration of Factor X was less uniformly changed and the results of the thromboplastin generation test showed much individual variation. In the 2 patients changes in thromboplastin generation did not run parallel with changes in the prothrombin time. Haemorrhagic episodes occurring when the prothrombin time was steady seemed to be linked with temporary serious depression of thromboplastin generation. The authors consider that both these tests should be used; they suggest that

unless there is substantial reduction in thromboplastin generation, the degree of hypocoagulability produced by the drugs is likely to be inadequate. M. C. G. Israëls

679. The Macroglobulinaemias. A Study of 30 Cases Confirmed by Ultracentrifugation. (Les macroglobulinémies. Étude sur 30 cas confirmés par ultracentrifugation)

E. ARON and R. VARGUES. *Presse médicale* [Presse méd.] 70, 1071-1074, May 5, 1962. 4 figs., 29 refs.

Macroglobulinaemia is considered to be present when the Sia reaction (precipitation in distilled water at a definite pH) is above 10%, but the authors, writing from the School of Medicine, Tours, France, point out that this reaction is subject to certain errors. They substituted for it, in their investigation of 30 cases, the reticulo-endothelial "double peak curve" devised by Sandor in 1958 (*C.R. Acad. Sci. (Paris)*, 1958, 246, 3547) and confirmed their results by ultracentrifugation. In the reticulo-endothelial diagram the level of the γ -euglobulins (those which precipitate at pH 7.4 in distilled water) is taken as the index of macroglobulinaemia. They can readily be isolated and show a close correlation with the molecular weight of the macroglobulins. Analysis by ultracentrifugation shows that the γ -euglobulins consist of several globulins with a sedimentation rate between 6 and 24. In oxalated blood they are considered responsible for the increase in erythrocyte sedimentation rate and also possibly for the prolongation of the coagulation time. All macroglobulinic sera show a viscosity higher than normal and increasing with a lowering of temperature; at +4° C. this hyperviscosity may increase, with formation of a gel, or diminish, with formation of a precipitate. The euglobulins and macroglobulins responsible for these phenomena are called cryoglobulins, and their presence, rather than that of autoantibodies, is considered responsible for cold agglutination.

The authors describe three clinical disorders associated with macroglobulinaemia: Waldenström's disease, Charcot's disease, and secondary macroglobulinaemia.

Waldenström's disease, first described in 1944, has a symptomatology similar to that of chronic lymphoid leucosis—asthenia, normochromic anaemia, moderate leucocytosis, adenopathy, enlarged spleen and liver. The adenogram shows lymphocytic monomorphism, and the myelogram proliferation of plasma-like lymphocytes. The erythrocyte sedimentation rate and the blood protein level are increased, the blood levels of total cholesterol and of fibrin are often decreased, and the blood levels of thromboplastin and of thrombin may be above normal. Some cases have haemorrhages in the skin, mucous membranes, and retina. The disease has a slow but eventually fatal course. It is regarded as the neoplastic type of macroglobulinaemia.

Charmot's disease, occurring chiefly in Africans, has certain features in common with Waldenström's disease, but with splenomegaly as its outstanding feature; adenopathy and haemorrhages are rare. It generally runs a chronic course. Paper electrophoresis shows a wide band of γ -globulin instead of the spot characteristic of Waldenström's disease, and the ultracentrifugation diagram shows a dome rather than a peak of macroglobulin. Charmot's disease is regarded as the inflammatory type of macroglobulinaemia.

The third type of macroglobulinaemia occurs secondarily to infectious disorders such as sleeping sickness, kala-azar, malaria, leprosy, and viral hepatitis. This variety of macroglobulinaemia, like Charmot's disease, differs from Waldenström's disease in its non-neoplastic character, but all three types have the common feature of dysproteinaemia.

In normal subjects the blood macroglobulin level is below 3%. Conventionally, however, macroglobulinaemia is not regarded as being present until the level is over 10%. The authors describe 9 cases with the clinical and cytological features of Charmot's disease, but with macroglobulin levels between 3% and 10%; they regard these as hypomacroglobulinic forms of Charmot's disease. They recall that certain types of haemorrhagic purpura with a disturbance of blood proteins have been designated by Di Guglielmo as "α-macroglobulinic macroglobulinaemia".

Macroglobulins are not *per se* regarded as pathological, but as representing a systemic disorder of a neoplastic or inflammatory nature.

Ethel Browning

680. The Human Small Lymphocyte: Its Possible Pluripotential Quality

K. CARSTAIRS. *Lancet* [*Lancet*] 1, 829-832, April 21, 1962. 4 figs., 14 refs.

The author, from St. George's Hospital, London, describes a technique suitable for the isolation from human blood of small lymphocytes almost free from other blood cells and reports the results of culturing them *in vitro*.

Heparinized blood was incubated with starch-coated iron particles; these are ingested by the granulocytes and monocytes, with resulting increase in their specific density so that they can be centrifuged out. Cells from the buffy coats were then resuspended in the supernatant plasma, and phytohaemagglutinin, which encourages erythrocyte sedimentation, was added. After standing for an hour in iced water the mixture was centrifuged at 20 g for 4 minutes. Aliquots of the resulting supernatant containing 500 to 1,000 nucleated cells per c.mm., of which 83% were small lymphocytes, 12% medium or large lymphocytes, 5% granulocytes, and less than 0.1% monocytes, were then cultured with twice their volume of TC 199 and 0.2 ml. of phytohaemagglutinin per 20 ml. blood equivalent. (TC 199 is a buffered salt solution containing most of the metabolic requirements for cell culture and also penicillin and streptomycin.) Subcultures to which demecolcine, which prevents mitosis proceeding beyond metaphase, had been added were examined periodically for 3 to 5 days.

In the first 24 hours the total nucleated-cell count showed little change, but subsequently declined by 10%. The proportion of small lymphocytes fell rapidly, being just under 5% at 48 hours and 1 to 2% at 72 hours; they were replaced by cells which were difficult to identify as typically lymphoid. In the first 24 hours there were many cells which resembled

medium lymphocytes. Mitosis began to be seen after 24 hours, and 5% of the cells were in mitosis after 48 hours. By then many of the cells resembled reticulum cells, plasma-blasts, or proerythroblasts; nucleoli were prominent. Between 68 and 86 hours 25% of the cells were in mitosis.

The results suggest that, in culture, small lymphocytes, possibly under the stimulus of phytohaemagglutinin, are capable of gradually transforming into larger cells apparently possessing the power to divide.

A. Ackroyd

MORBID ANATOMY AND CYTOLOGY

681. Histiocytic Medullary Reticulosis

E. GREENBERG, D. M. COHEN, G. L. PEASE, and R. A. KYLE. *Proceedings of the Staff Meetings of the Mayo Clinic* [*Proc. Mayo Clin.*] 37, 271-283, May 9, 1962. 4 figs., 19 refs.

Histiocytic medullary reticulosis is a rapidly fatal form of reticulosis characterized clinically by pyrexia, loss of weight, hepatosplenomegaly, lymphadenopathy, anaemia, and frequently leucopenia, thrombocytopenia, and jaundice. Histologically there is a systematized proliferation of histiocytes with active erythrophagocytosis. The disease is rarely diagnosed during life, although this can be done on the haematological findings. Since the disease was first described in 1939, 47 cases have been reported. In this paper the authors report a further case, which, they state, is the first to be diagnosed ante mortem in the U.S.A. Analysis of the features of this case and those reported in the literature showed that the disease occurs most commonly in the fourth, fifth, and sixth decades of life and males are affected three times more frequently than females. The onset is usually acute with weakness, malaise, and rapid loss of weight. The course is rapid, two-thirds of the patients dying within 6 months. Pyrexia is practically always present, the temperature at times reaching 106° F. (41.1° C.). Jaundice, which occurs in nearly half the cases, is of mixed parenchymatous and obstructive type. Oedema and serous effusions are common and haemorrhage from and into various tissues frequently occurs. Liver, spleen, and lymph-node enlargement of slight or only moderate degree is found. A progressive normocytic and normochromic anaemia develops; it is of obscure origin and may be partly haemolytic. The platelet count is usually very low and the leucocytic count varies. The most distinctive haematological abnormality is seen in the differential leucocyte count. This consists in the presence of reticulum cells and atypical mononuclear cells, which may represent 15 to 18% of the total. The characteristic microscopical findings are increased numbers of mature and immature histiocytes with moderate mitotic activity and erythrophagocytosis in the sinusoids of the spleen, liver, and some lymph nodes and in the bone marrow, this last abnormality permitting ante-mortem diagnosis by means of marrow puncture.

R. Wyburn-Mason

682. Diagnosis of Hodgkin's Disease by Liver Biopsy

M. MACLEOD and A. L. STALKER. *British Medical Journal* [*Brit. med. J.*] 1, 1449-1451, May 26, 1962. 4 figs., 18 refs.

Writing from the University of Aberdeen, the authors point out that histological examination of lymph nodes is not always conclusive in the diagnosis of Hodgkin's disease, especially in cases in which the superficial nodes are unaffected or show only reactive hyperplasia, while features

such as hepatic enlargement or splenomegaly (but without lymphadenopathy) or haemolytic anaemia may be prominent, or pyrexia and fatigue may simulate an infection or a "collagen disease". Involvement of the liver is common in Hodgkin's disease; the histological picture consists of infiltration of the portal spaces by reticulum cells, plasma cells, round cells, polymorphonuclear leucocytes, and fibroblasts, occasionally with an appearance suggesting sarcoidosis.

The authors describe 11 cases of Hodgkin's disease in which the diagnosis could not be established by examination of a superficial lymph node, but in which aspiration biopsy of the liver gave valuable information. The series included 2 cases of haemolytic anaemia. In one of these, in which the anaemia was acute, the liver biopsy showed haemosiderosis and extramedullary haematopoiesis; in the other, in which the anaemia was more chronic and there was terminal intrahepatic biliary stasis, the diagnosis of Hodgkin's disease was confirmed at necropsy 3 years later. Aspiration liver biopsy was also helpful in 2 cases of obstructive jaundice due to intrahepatic cholestasis occurring in the later stages of Hodgkin's disease.

The liver is most likely to be involved in the cases in which deep structures are primarily affected, in which symptoms do not appear until the condition becomes generalized and in which diagnosis in the early stages is consequently difficult; in such cases a normal or only slightly raised serum bilirubin level with increased phosphatase activity indicates that liver biopsy is likely to be helpful. Aspiration biopsy of the liver is without risk or discomfort to the patient if essential precautions are taken. The authors, using the technique introduced by Terry in 1949 (*Brit. med. J.*, 1949, 1, 657), have performed 300 such biopsies in the investigation of cases showing features similar to but not intrinsically those of Hodgkin's disease.

Ethel Browning

683. The Pathologic Anatomy and Pathogenesis of Fatal Human Leptospirosis (Well's Disease)

V. M. AREAN. *American Journal of Pathology* [*Amer. J. Path.*] 40, 393-423, April, 1962. 25 figs., bibliography.

The clinical and the gross and microscopical findings at necropsy in 33 cases of leptospirosis are described in this paper from the College of Medicine, University of Florida, Gainesville. Except for a child of 5 years, the ages of the patients, 11 of whom were coloured, ranged from 15 to 73 years. Most of them lived in houses heavily infested with rats; others worked in canals, sewers, harbours, or sugar plantations where they were likely to be exposed to infection. The clinical symptoms varied, but fever was noted in all cases and jaundice in all except one. Of the 33 patients, 31 complained of severe cephalalgia and profound prostration. Myalgia, muscle tenderness, anorexia, and nausea and vomiting were present in about half, renal insufficiency was a fairly frequent symptom, and all except one of the patients had cardiovascular collapse.

At necropsy jaundice was present in 32 patients and haemorrhages, chiefly as petechiae, were invariably present and involved most organs and tissues. Liver enlargement was observed in about half the cases and hypertrophy of the heart in 12. Damage to the capillary wall rather than changes in the blood clotting mechanism was considered to be responsible for the haemorrhagic diathesis. The hepatic lesions were typical, but the severity varied and depended, in part, on the duration of the disease. Renal insufficiency

was primarily the result of tubular damage, occurring in a segmental fashion and associated with other features suggesting hypoxic nephrosis as the basic mechanism.

Interstitial nephritis (25 patients) was found to be a manifestation of the later stages of the disease and secondary to necrosis of the tubular epithelium and disruption of the basement membrane. The author reviews the various theories concerning the pathogenesis of leptospirosis and states that the clinical and histological changes strongly suggest that a toxin is the mechanism of leptospiral pathogenicity. Although *Leptospira icterohaemorrhagiae* has not been demonstrated to possess a toxin, the course of the disease is considered to support the view that a toxic product released by lysis is responsible for the course of the disease.

Edward Hindle

684. The Kupffer Cell Reaction in Murine and Human Viral Hepatitis, with Particular Reference to the Origin of Acidophilic Bodies

B. RUEBNER and K. MIYAL. *American Journal of Pathology* [*Amer. J. Path.*] 40, 425-435, April, 1962. 11 figs., 23 refs.

The principal object of the investigation here reported from the Johns Hopkins Hospital and University, Baltimore, was to decide whether the initial damage in viral hepatitis occurs in endothelial or in parenchymal cells. A 10% suspension of the mouse hepatitis virus was inoculated intravenously into 30 female mice, which were then killed in groups of 5 at daily intervals. The evolution of the hepatitis was followed in serial 1- μ thick sections. The earliest lesion appeared in the Kupffer cells, which showed mitotic figures, nuclear pyknosis, karyorrhexis, fragmentation, and hyalinization. It was possible to trace transitions between the hyaline cells and globular acidophilic bodies which appeared later. At this early stage, parenchymal cell necrosis was minimal; it developed long after the Kupffer cell changes.

In a second experiment, indian ink was introduced intravenously in order to label Kupffer cells before inoculation with murine hepatitis virus. Particles of indian ink were found in Kupffer cells and in occasional acidophilic bodies, but not in parenchymal cells. Damage to Kupffer cells thus preceded alterations in parenchymal cells. Moreover, injured Kupffer cells were apparently transformed into acidophilic bodies.

Examination of biopsy specimens from human subjects with viral hepatitis showed a Kupffer cell reaction closely resembling that seen in the murine disease. It seemed possible to trace transitions between swollen Kupffer cells, hyalinized Kupffer cells, and eosinophilic bodies. It is concluded that in human viral hepatitis, as in the murine disease, injury of Kupffer cells may be a primary event and acidophilic bodies ("Councilman bodies") may subsequently develop from these cells.

D. Geraint James

685. Liver Damage after Chemotherapy for Leukemia and Lymphoma

G. D. AMROMIN, R. M. DELIMAN, and E. SHANBROM. *Gastroenterology* [*Gastroenterology*] 42, 401-410, April, 1962. 8 figs., 10 refs.

Of 139 patients dying from lymphoma and leukaemia and coming to necropsy 22 (16%) who had received cytostatic agents and who had developed jaundice were studied at the

City of Hope Medical Center, Duarte, California. In 12 of these patients there was some lesion, such as obstruction to bile flow by the tumour, that alone might have caused the jaundice. In the remaining 10 cases, however, the aetiology of the jaundice was less apparent, but there did seem to be a time-sequence relation between drug administration and the clinical appearance of jaundice or abnormal laboratory findings, or both. These 10 patients had been treated primarily or exclusively with cytostatic drugs and in all the liver showed degenerative and cholestatic changes. Thus in the livers of all 6 patients who had received chlorambucil there was a generalized decrease or complete absence of intracellular glycogen, and only a slight to moderate degree of liver regeneration. In 3 of these cases it was considered (by exclusion of other possible factors) that chlorambucil was the primary cause of the jaundice, while in 3 others the jaundice was thought to have resulted from a combination of hepatocellular damage (possibly chlorambucil-induced) and other factors (bacteraemia in 2 cases and partial obstruction in one). In 2 further patients who had received 5-[bis(2-chlorethyl)amino]uracil (U-8344) some liver cells showed degenerative changes with glycogen infiltration of the nuclei. One jaundiced patient had received 6-azouracil and 6-mercaptopurine, and another 6-mercaptopurine and methotrexate; in both cases centrilobular degenerative changes and focal necrosis were observed in the liver.

Summing up, the authors emphasize the inherent difficulty of implicating a particular substance as the sole factor responsible for liver damage, bearing in mind the multiplicity of potentially hepatotoxic factors to which a patient is exposed. It seems, however, that cytostatic agents may be important contributing factors.

H. Caplan

686. Studies on Chronic Glomerulonephritis. II. A Concept of the Morphogenesis of the Disease Based on Light and Electron Microscopic Observations

J. W. STEINER, H. Z. MOVAT, E. R. YENDT, and R. J. SLATER. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 195-206, Feb. 3, 1962. 19 figs., 9 refs.

In a previous paper (*Canad. med. Ass. J.*, 1962, 86, 153) an analysis was presented of the fine structure of the intracapillary changes in the free portions of capillary loops in chronic glomerulonephritis. In the present paper from the University and the Hospital for Sick Children, Toronto, the authors correlate the light and electron microscope appearances of these changes. They examined 25 needle-biopsy specimens of the kidney from patients with a clinical diagnosis of chronic glomerulonephritis, sections being stained with periodic acid-silver methenamine (P.A.S.M.).

Under the light microscope the capillary basement membranes were found to be irregularly thickened. In axial areas varying quantities of P.A.S.M.-negative aggregates were distributed in pools and islands between and within axial cells. These intracapillary deposits appeared to become increasingly argentophil the more diffuse and extensive the process. With increasing deposit formation the number of cells increased in the capillaries in a centripetal direction. These processes led to a progressive narrowing of the capillary loops, the result being a solid capillary with a recognizable basement membrane, the interior being filled with a variable mixture of endothelial nuclei and P.A.S.M.-positive material. Many obsolete glomeruli were seen but

they were so distorted that interpretation in terms of individual component changes was not possible.

As seen under the electron microscope the intracapillary alterations consisted of two components. The changes in the free portion of the loops were described in detail in the previous paper. The axial reaction corresponded to the alterations seen by the light microscope, whereby axial regions assumed an increasing degree of cellularity and of P.A.S.M. positivity. The final phase of the axial reaction consisted of the encroachment of axial regions on marginal capillary loops. The processes of endothelial proliferation, formation of basement-membrane-like deposits, thickening of the lamina densa, and the axial reaction blended to produce a picture of solid lobules bounded on the outside by a thickened basement membrane.

The authors point out that the variable severity of the intracapillary changes as seen in any given case needs to be emphasized. Not only are obsolete and almost intact glomeruli found side-by-side, but also great variations are seen from loop to loop and within individual capillaries. It is assumed that this represents a progression from almost intact to obsolete loops, the intermediate stages being represented by the various greater and lesser alterations seen in others. This seems justified, since observations with the light microscope show that the later lesions of obsolescence increase in number with the prolongation and increasing gravity of the disease.

G. Clayton

687. The Kidney in Rheumatoid Arthritis: Studies by Renal Biopsy

V. E. POLLAK, C. L. PIRANI, I. E. STECK, and R. M. KARK. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 1-9, Feb., 1962. 30 refs.

The clinical findings and the results of biopsy examination of the kidney in 41 patients with rheumatoid arthritis are reported in this paper from the University of Illinois College of Medicine, Chicago. The patients selected had longstanding rheumatoid arthritis with marked deformities, or rheumatoid disease associated with proteinuria, or had received gold therapy. Steroids had been administered in 21 cases.

Biopsy examination showed no histological abnormality in 21 cases. Arterio- or arteriolosclerosis or arteriolar nephrosclerosis was seen in 14 of the older patients (average age 50 years). In 4 cases biopsy revealed amyloidosis and in 2 lupus nephritis. Glomerulitis, as previously seen by other workers at necropsy, was not noted in any of the biopsy specimens. This condition, which consists in mild endothelial hyperplasia of all or nearly all glomeruli, is therefore presumed to be a late manifestation. Persistent proteinuria was found in 13 cases; biopsy examination in these cases showed amyloidosis in 4, lupus nephritis in 2, and arteriolar nephrosclerosis in 2. In 2 others there was vascular sclerosis, but no interstitial or glomerular lesions were seen. Renal function was within normal limits in nearly all these cases. Of the 18 patients receiving gold salts, 4 had proteinuria, but the histology was normal in 17; the histological changes in the remaining patient were of doubtful significance.

The authors consider that proteinuria should not be attributed to rheumatoid involvement of the kidney, and that serious renal disease in rheumatoid arthritis is most commonly caused by amyloidosis.

G. Loewi

Microbiology and Parasitology

688. Isolation of Poliovirus from Spinal Fluid

L. SMITH. *Journal of Laboratory and Clinical Medicine* [J. Lab. clin. Med.] 59, 490-495, March, 1962. 5 refs.

During an epidemic of poliomyelitis in New Haven, Connecticut, in 1959 poliomyelitis virus Type 1 was isolated at the Department of Epidemiology and Public Health, Yale University, from the cerebrospinal fluid (C.S.F.) of 3 out of 22 patients, by means of primary monkey kidney cell cultures; in each case virus was later re-isolated from the original specimen. The positive specimens, which contained from $10^{2.5}$ to 10^4 TCD₅₀ per ml. of C.S.F., were taken between the 2nd and 7th days of the illness, the 3 patients being children aged 6, 13, and 17 months respectively who were all excreting virus.

The author notes that although other enteroviruses, such as Coxsackie and E.C.H.O. viruses, have been isolated frequently from the C.S.F., the isolation of poliovirus has previously been reported on only 3 occasions—from one out of 37 cases tested by McCrea (*Pediatrics*, 1957, 19, 869) and from 2 out of 32 examined by Johnson *et al.* (*Amer. J. Hyg.*, 1960, 71, 331). The present higher rate of isolation was not apparently related to the degree of neurological involvement, for although one child suffered a fatal bulbo-spinal poliomyelitis and one developed paralysis, the third showed no muscular weakness at all. However, the highest incidence of disease during the epidemic was in infants and young children and it is possible that the prevalent strain of virus was unusually virulent.

Janice Taverne

689. The Effect of Trachoma Virus Vaccine on the Course of Experimental Trachoma Infection in Blind Human Volunteers

J. T. GRAYSTON, SAN-PIN WANG, YEN-FEI YANG, and R. L. WOOLDRIDGE. *Journal of Experimental Medicine* [J. exp. Med.] 115, 1009-1022, May 1, 1962. 13 figs., 22 refs.

The authors of this paper from United States Naval Medical Research Unit No. 2, San Francisco, and the National Taiwan University, Taipei, inoculated one conjunctiva of each of 6 blind human volunteers in Taiwan with a local strain (TRIC-Taiwan-1-1958) of elementary body virus isolated from a patient with trachoma. Virus material, derived from the 7th passage in embryonated hen eggs, produced the clinical picture of trachoma in every inoculation, even at the dilution of 10^{-4} of infected yolk sacs. There was an initial acute follicular conjunctivitis with sero-suppurative discharge, petechial haemorrhages of the conjunctiva, and tender pre-auricular lymph nodes. Follicles in the bulbar conjunctiva were still present 5 months after infection. Thereafter, decrease in the acute changes was accompanied by the appearance of chronic changes, with epithelial keratitis and pannus, gelatinous follicles, and eventual cicatrization of the conjunctiva. These clinical findings were supported by repeated demonstration of typical inclusion bodies of Halberstaedter-Prowazek in conjunctival and even in corneal cells, by repeated re-isolation of elementary body virus in egg yolk sacs, and by the development of complement-fixing antibody with a "specific"

trachoma antigen in each volunteer. Control inoculations with adenovirus Type 4 and with normal yolk sac gave different clinical and laboratory findings.

Towards the end of the 2nd month of the experiment, when the trachomatous changes were well established, 3 of the volunteers received a series of 6 intramuscular injections of trachoma vaccine prepared from both TW-1 and TRIC-Taiwan-3-1959, while the other 3 received placebo injections. The ophthalmologist assessing the clinical findings was unaware of the identity of the volunteers who received vaccine and placebo respectively. The vaccine led to an antibody response and to modification of the disease. While the 3 volunteers who received placebo each developed cross-infection of the uninoculated eye and had an acute reactivation of the bilateral disease after withdrawal of treatment with an antibiotic ointment, the vaccinated subjects remained free of infection in uninoculated eyes and had no relapse after discontinuance of ointment therapy. The reactivated disease responded rapidly to oral sulphonamide treatment.

The conclusion is that "humoral antibodies develop during the course of experimental trachoma eye infections and that vaccine made from trachoma virus favorably affects the course of these infections".

D. Geraint James

690. Vaccinal Keratitis Treated with Interferon

B. R. JONES, J. E. K. GALBRAITH, and M. K. AL-HUSSAINI. *Lancet* [Lancet] 1, 875-879, April 28, 1962. 1 fig., 6 refs.

Interferon, prepared in monkey-kidney cell cultures, was applied half-hourly during waking hours in 5 cases of vaccinal keratitis presenting (at Moorfields Eye Hospital, London) with granular epithelial opacification and ulceration. In all instances granular opacification of the epithelium resolved within 24 hours, and ulceration started to heal after interferon therapy was begun. Whereas topical interferon therapy appears to display antiviral activity on the epithelial stages of human vaccinal keratitis, it does not appear to influence the later stromal stages. In all cases, whether treated with interferon or by epithelial débridement, epithelial keratitis was followed by stromal oedema and diffuse infiltration. As this receded, punctate superficial stromal opacities appeared, usually in a ring of 5 to 6 mm. diameter. Vaccinal corneal ulcers can assume linear or map-like shapes with linear or branching extensions that may resemble herpetic keratitis. Vaccinal conjunctivitis may be associated with pre-auricular or submandibular adenitis, and should be remembered as a cause of non-follicular oculo-glandular syndrome with a polymorphonuclear exudate.

D. Geraint James

691. Investigations on Hospital Infection. (Untersuchungen über Hospital-Infektionen)

H. HACKL. *Medizinische Welt* (Stuttgart) [Med. Welt (Stuttg.)] 1144-1148, No. 20, May 19, 1962. 18 refs.

Writing from the Am Steinhof Hospital, Vienna, the author discusses the emergence of antibiotic-resistant staphylococci and quotes reports from the literature in support of

and against the existence of so-called "hospital staphylococci" which are alleged to show higher resistance to antibiotics than do those found outside hospitals. He suggests that the contradictory results obtained are due to differences in the methods employed, to incorrect planning of experiments, or to faulty statistical evaluation.

In the present study the author examined 600 strains of staphylococci isolated from hospital patients and 50 from patients seen in general practice. The two groups of patients were identical in respect of clinical diagnosis, nature of specimens, and relative sensitivity of the accompanying organisms, but the proportion of haemolytic staphylococci was higher in the hospital patients. Sensitivity was tested by a ditch-plate technique on the following antibiotics: bacitracin-neomycin, chloramphenicol, erythromycin, penicillin, streptomycin, and tetracycline; and also on sulphaphenazole. An Oxford strain of staphylococcus was used as the reference organism. Sensitivity was graded from 1 (highly sensitive) to 5 (completely resistant).

A table presents the mean values for resistance to each drug, subdivided for haemolytic and non-haemolytic organisms, and each column is again subdivided into hospital and domestic staphylococci. T-test values were calculated to assess the significance of the differences found. In general, there was no difference except that hospital haemolytic staphylococci showed significantly less resistance to bacitracin-neomycin and to chloramphenicol than did those from general practice, while hospital non-haemolytic staphylococci were less resistant, and to a highly significant degree, to sulphaphenazole.

F. Hillman

692. A Defined Agar Medium for Genetic Transformation of *Neisseria meningitidis*

B. W. CATLIN and G. M. SCHLOER. *Journal of Bacteriology* [J. Bact.] 83, 470-474, March [received May], 1962. 14 refs.

At Marquette University, Milwaukee, Wisconsin, the authors have prepared a defined agar medium containing 8 inorganic salts in addition to sodium citrate, sodium lactate, arginine, cysteine, glycine, and sodium glutamate which, they report, enabled *Neisseria meningitidis*, Strain No. 15, to grow well and to develop as many surface colonies as formed on a conventional complex nutrient solid medium, in both cases without additional help from increased pressure of carbon dioxide. [For exact details of the defined medium the original paper should be consulted.]

When populations of this strain were placed for 15 or 30 minutes in a solution of transforming deoxyribonucleic acid derived from a streptomycin-resistant strain of the organism the transformation rate to streptomycin resistance was 0.1 to 0.3% of the bacterial cells so exposed.

K. Zinnemann

693. Studies of Active Immunization against Enteropathogenic *Escherichia coli*

F. TURGEON, A. G. BORDUAS, and A. FRAPPIER. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 767-771, April 28, 1962. 14 refs.

This paper from the University of Montreal concerns the mouse-immunizing potency of various fractions of enteropathogenic *Escherichia coli*.

The following fractions of *E. coli* Strains O26:B6, O55:B5, O111:B4, and O127:B8 were used: (1) the filtered super-

natant of a 5-hour broth culture, (2) the filtered saline washings of this culture, (3) the washed culture, and (4) whole culture. For each strain studied, 4 groups of 66 mice were immunized. The control groups, 66 mice in each group, were injected with the non-enteropathogenic *E. coli* strain or with trypticase soy broth.

A table shows the doses of the 8 immunizing injections given to each animal. The animals were challenged 18 days after the last immunizing dose by intracerebral injections of 0.03 ml. of different dilutions, chosen around the expected LD₅₀, of a whole culture. The LD₅₀ of the immunized animals was then compared with that of the non-immunized controls and the degree of protection found expressed in multiples of the LD₅₀.

All the different fractions of Strains O55:B5 and O111:B4 gave 20 to 49 LD₅₀ protection. A similar result was obtained after repetition of the experiment with more stringent controls. Mice vaccinated with non-enteropathogenic *E. coli* in this last series were found to be protected to the extent of 9 LD₅₀ against Strain O55:B5 and this is probably due to the presence of antigens common to both strains.

This work points to the possibility of immunization against *E. coli* O55:B5 and O111:B4 by non-toxic, soluble antigens, and it is suggested that these may be used in pregnant mothers to protect the newborn infant against infantile diarrhoea. The other two strains—namely, O26:B6 and O127:B8—need further investigation.

F. Hillman

694. Incidence of Heterologous Antibodies in Virus-confirmed Cases of Poliomyelitis

T. FRANCIS JR. and G. C. BROWN. *New England Journal of Medicine* [New Engl. J. Med.] 266, 642-644, March 29, 1962. 9 refs.

The results of the original field trial of Salk-type poliomyelitis vaccine carried out by the first-named author and others in 1957 showed that about two-thirds of paralytic cases of poliomyelitis occurred in patients who had no neutralizing antibody to any of the three types of virus. In the present study, therefore, the presence of antibody to the two types of virus heterologous to the type isolated was determined in cases of the disease occurring in the Detroit epidemic of 1958 among subjects who had been vaccinated, and was used as an index of the adequacy of vaccination.

Of 126 unvaccinated patients 21 (16%) had both types of heterologous antibody, as compared with 13 out of 37 (35%) of vaccinated patients. Of cases with severe paralysis, 2 (18%) of 11 vaccinated patients had both types of heterologous antibody, compared with 6% among unvaccinated patients. When heterologous antibody against only one type was present it was usually against Type 2—the type causing most subclinical infections, as well as being the most potent type in the vaccine. The absence of heterologous antibody among these vaccinated cases suggests either that a false history of vaccination was given or that the antigenic stimulus was not effective. The authors, who write from the University of Michigan, Ann Arbor, conclude that the severity of paralysis among vaccinated persons was definitely less than among the unvaccinated, and resulted in fewer deaths and a larger number of complete recoveries. They suggest that those cases of disease which did occur among the vaccinated seem to have been due to a failure of antibody response, especially to poliomyelitis virus Types 1 and 3.

Janice Taverne

Pharmacology and Therapeutics

695. **The Mechanism of Action of Guanethidine.** (Untersuchungen zum Wirkungsmechanismus des Guanethidins) G. KRONEBERG, H. J. SCHÜMANN, and A. ECKARDT. *Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie* [Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.] 243, 16-25, 1962. 4 figs., 18 refs.

The object of this investigation was to ascertain whether there is a relationship between the inhibitory effect of guanethidine on the sympathetic nervous system and the depletion of catechol amines. It was carried out at the Pharmacological Institute, Frankfurt, on cats, on the isolated atrium of guinea-pigs, on normotensive rats, and on rats made hypertensive by ligation of one kidney and removal of the other. The catechol amine content of extracts of the adrenal glands was determined colorimetrically and that in extracts of brain and heart fluorimetrically.

In cats and dogs guanethidine initially stimulated the sympathetic nerves, and in anaesthetized cats the effect of the drug in a dosage of 5 to 10 mg. per kg. body weight on the blood pressure and nictitating membrane was not diminished after adrenalectomy. In the isolated guinea-pig atrium 200 to 800 μ g. of guanethidine also had a sympathicomimetic effect which proved to be like that of tyramine, being abolished by cocaine and by pre-treatment of the guinea-pig with reserpine. Determination of the catechol amines (CA) of the isolated atria after administration of guanethidine showed that this drug inhibits the tyramine-induced liberation of CA in two ways: (1) in acute experiments the inhibition was not associated with a depletion of CA and was reversible by washing out the guanethidine; (2) after treatment of the animals with guanethidine (30 mg. per kg. intraperitoneally) 24 hours before the tests on the isolated atrium, the CA content was reduced to about 20% of the control value and now the effect was not reversible by washing out the guanethidine. In rats, guanethidine (2 to 10 mg. per kg. intravenously) greatly reduced the pressor effect of tyramine and methylamphetamine and increased the effect of noradrenaline. In rats with renal hypertension, the drug reduced the blood pressure significantly, and the CA content of the heart was reduced to about 50%, while that of the adrenal glands and brain remained practically unchanged. In normotensive rats the same dose of guanethidine had no effect on the blood pressure, though in this group there was also marked reduction in the content of catechol amines of the heart. A. Schott

696. **The Influence of Guanethidine and Bretylium on the Liberation of Pyrocatechol Amines.** (Der Einfluss von Guanethidin und Bretylium auf die Freisetzung von Brenzcatechinaminen)

A. PHILIPP and H. J. SCHÜMANN. *Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie* [Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.] 243, 26-35, 1962. 4 figs., 19 refs.

In the study reported above [see Abstract 695] the authors established that, contrary to the view expressed by Cass et al. (*Proc. Soc. exp. Biol. (N.Y.)*, 1960, 103, 871), guanethidine

may inhibit the release of noradrenaline without causing any significant depletion of this compound in tissues innervated by the sympathetic nervous system. In order further to clarify the mechanism of this inhibition, the effect of guanethidine and bretylium on the release of catechol amines was investigated on isolated, perfused ox adrenal glands and isolated chromaffin granules and also on the atria of guinea-pigs.

In the adrenal glands the release of catecholamines produced by carbachol ("doryl"), nicotine, and phenylethylamine was inhibited by 0.4 μ mol of guanethidine; bretylium proved less active and did not inhibit the effect of phenylethylamine. In high doses (30 μ mol) both guanethidine and bretylium released catechol amines. Since both these compounds are local anaesthetics their action also was compared with that of amethocaine and cocaine, which were found also to abolish the effect of carbachol, nicotine, and phenylethylamine, whereas the ganglion-blocking agent chlorisondamine chloride ("ecolid") inhibited only the effect of carbachol and nicotine, but not that of phenylethylamine. From isolated chromaffin granules guanethidine released catechol amines, their amount depending on the dosage of the drug; it did not, however, inhibit the releasing effect of phenylethylamine. On the isolated guinea-pig atria guanethidine, cocaine, and amethocaine inhibited the effect of nicotine and tyramine, but ecolid only that of nicotine. It is concluded that, apart from its ganglion-blocking and local anaesthetic effects, guanethidine, as distinct from bretylium, has also a marked effect on the cell membrane, producing a reduction in its permeability. A. Schott

697. **The Effect of Guanethidine on the Skeletal Musculature and the Spinal Reflexes.** (Über eine Wirkung von Guanethidin auf Skelettmuskulatur und Rückenmarkreflexe) G. KRONEBERG and K. STOEPEL. *Naunyn-Schmiedeberg's Archiv für experimentelle Pathologie und Pharmakologie* [Naunyn-Schmiedeberg's Arch. exp. Path. Pharmak.] 243, 36-43, 1962. 5 figs., 13 refs.

Starting from the observation that guanethidine inhibits polysynaptic and monosynaptic reflexes in cats, the present investigation was undertaken at the Pharmacological Institute, Frankfurt, to determine whether the site of action of the compound in cats is the spinal cord, the neuromuscular synapse, or the muscle itself. The reflexes studied were the polysynaptic homolateral flexor and crossed extensor reflexes, and the monosynaptic knee-jerk reflex; also examined were the indirect stimulation of muscle (peripheral end of the sciatic nerve) and direct stimulation of the gastrocnemius. Transection of the spinal cord was also performed at the level of D11-12, in some experiments with and in others without decerebration.

It was shown that guanethidine (10 mg. per kg. body weight) inhibited both polysynaptic and monosynaptic reflexes, whereas indirect stimulation of muscle was depressed only transiently and to a smaller extent. After the intra-arterial injection of guanethidine, indirect and reflex stimulation were both inhibited immediately. It is tenta-

tively concluded that guanethidine acts on muscle beyond the neuromuscular synapse and, in addition, on the synapse itself. Both actions, however, require a high concentration of the drug, of the order of 10 to 20 times that necessary for its therapeutically important action on the adrenergic nervous system.

A. Schott

698. A Comparison between Aspirin and Antibiotics in the Treatment of Minor Respiratory Infections

P. K. FRASER, L. A. HATCH, and K. E. A. HUGHES. *Lancet* [Lancet] 1, 614-616, March 24, 1962. 12 refs.

A double-blind trial of aspirin, phenoxymethylpenicillin, and oxytetracycline in the treatment of acute upper respiratory tract infections was carried out on patients admitted to the Royal Naval Hospital, Haslar, Portsmouth, the object being to determine whether antibiotics altered the course of these common infections and whether complications were prevented.

A total of 600 patients who were admitted consecutively were subjected to bacteriological and virological investigation. Certain patients were eventually excluded—namely, those with complications at the time of entry, patients with conditions requiring special treatment, such as streptococcal infections and glandular fever, and patients with serological evidence of virus infection.

Of the original 600, 295 remained, and of these 95 were treated with aspirin, 96 with phenoxymethylpenicillin, and 104 with oxytetracycline. There was no evidence in these patients that either antibiotic had any advantage over aspirin so far as complications or other clinical criteria were concerned.

John Fry

699. Modern Pharmaco-therapeutic Possibilities in the Treatment of Pain. Experiments with Ethoheptazine. (Moderne possibilità farmaco-terapeutiche nella cura del dolore. Esperimenti con l'ethoheptazina)

P. CINELLI and M. ZUCCHINI. *Minerva medica* [Minerva med.] 53, 637-642, March 3, 1962. 19 refs.

Ethoheptazine ("zactane"), a newly synthesized morphine-like analgesic substance, was tried in 75 patients attending the Medical Department of the University of Florence. It was found that 150 mg. of ethoheptazine had an effect similar to that of 30 mg. of codeine phosphate. The analgesic action began in about half-an-hour, rapidly reached a maximum, and remained constant for 4 to 5 hours. The combination of 75 mg. of ethoheptazine with 325 mg. of aspirin gave "optimal" results in 54% of patients in the hospital and in 77% of ambulatory patients.

Side-effects, consisting of digestive disturbances and, more rarely, itching and vertigo, were observed in about 10% of the patients, but they could be reduced by diminishing the dose; the treatment had to be discontinued in only one patient. The best results were obtained with a dosage of 75 mg. 3 to 4 times a day.

A. J. Karlish

700. Objective Evidence of Mental Effects of Heroin, Morphine and Placebo in Normal Subjects

G. M. SMITH, C. W. SEMKE, and H. K. BEECHER. *Journal of Pharmacology and Experimental Therapeutics* [J. Pharmacol. exp. Ther.] 136, 53-58, April, 1962. 2 figs., 16 refs.

Comparative effects of morphine, heroin and placebo on performance on tests of mental functions were studied in nonaddicted male college and graduate students between

21 and 32 years of age. In one study 24 subjects were given 10 mg. of morphine phosphate and 1 ml. of normal saline, subcutaneously, on separate occasions. In another study 24 different subjects were given morphine phosphate (10 mg.), heroin hydrochloride (4 mg.) and placebo, also on separate occasions. The medications were given on a body weight basis; the doses were for the salts per 70 kg. of body-weight. Order of drug administration was balanced in each study. The double unknowns procedure and other necessary controls were used. Each experimental day a subject was given two batteries of tests, each battery consisting of a series of tests. The tests, testing procedures and methods of data evaluation have been described.

On the basis of the objective data reported above the following conclusions are drawn: (1) Heroin (4 mg.) and morphine (10 mg.) can produce statistically significant impairment of certain aspects of mental performance, and the overall effect of each drug is definitely one of mental impairment. (2) The impairment is primarily one of speed rather than accuracy. (3) The impairment produced by 4 mg. of heroin appears earlier and is somewhat greater than that produced by 10 mg. of morphine. (4) Significant mental impairment can be demonstrated as early as 40 minutes and as late as 5 hours and 40 minutes after administration of 10 mg. of morphine.—[Authors' summary.]

701. Thalidomide and Congenital Abnormalities

M. C. JOSEPH. *Developmental Medicine and Child Neurology* [Develop. Med. Child Neurol.] 4, 338-339, June, 1962. 1 fig., 11 refs.

702. Cross Tolerance between Mescaline and LSD-25. With a Comparison of the Mescaline and LSD Reactions. [In English]

A. B. WOLBACH JR., H. ISBELL, and E. J. MINER. *Psychopharmacologia* [Psychopharmacologia (Berl.)] 3, 1-14, 1962. 2 figs., 22 refs.

This study was carried out at the Addiction Research Center of the U.S. Public Health Service, Lexington, Kentucky, to compare the effects of lysergic acid diethylamide (LSD-25) and mescaline in the same subject and to measure the tolerance and cross-tolerance to these drugs. It is now well established that the clinical syndromes produced by mescaline and LSD-25 are very similar despite the differences in the chemical structure of the two drugs. For the first test 10 subjects (former opiate addicts) were given equivalent doses of LSD and mescaline by intramuscular injection. Detailed observations on autonomic activity and behaviour were then made and these together with the replies to a questionnaire were analysed statistically. In the second part of the study the same patients were given increasing doses of both drugs in a "cross-over" trial and similar detailed observations again made.

It was found that the objective and subjective changes induced by LSD and mescaline were very similar when the drugs were given in dosages of 1.5 and 5 mg. per kg. body weight respectively, though the effects of mescaline persisted longer. It was observed that patients who received LSD daily developed a direct tolerance to the drug and also a cross-tolerance to mescaline, while similarly patients receiving mescaline daily became tolerant to this drug and cross-tolerant to LSD. The authors conclude that it seems likely that LSD and mescaline have similar actions because of some common biological mechanism.

B. M. Davies

Chemotherapy

ANTIBIOTICS

703. Fucidin: a New Orally Active Antibiotic

W. GODTFREDSEN, K. ROHOLT, and L. TYBRING. *Lancet* [Lancet] 1, 928-931, May 5, 1962. 1 fig., 3 refs.

The isolation of a new antibiotic, fusidic acid, from the fermentation broth of *Fusidium coccineum* has recently been reported (*Nature (Lond.)*, 1962, 193, 987). In experiments at the Laboratories of Leo Pharmaceutical Products, Copenhagen, the sodium salt, "fucidin", was shown to be highly active *in vitro* against Gram-positive bacteria and *Neisseria* and to have negligible activity against Gram-negative organisms and fungi. Staphylococci were particularly susceptible. The *in-vitro* activity of the compound was greater at acid pH values and was considerably reduced in the presence of serum. Under certain conditions fucidin was synergistic with phenoxymethylpenicillin. Resistant strains developed rapidly on culture in the presence of the drug. Acute toxicity was low, the LD₅₀ being 975 mg. per kg. when the drug was administered orally to mice; in rats given 200 mg. per kg. daily for 24 weeks there were no detectable changes in the organs examined at necropsy. Studies in human volunteers given 500 mg. by mouth 3 times a day for 4 days showed that the drug accumulated in the serum, was widely distributed in the tissues, and was not excreted in recognizable form in the urine. To date a variety of staphylococcal infections in 300 patients have been treated with fucidin without serious toxic reactions.

F. W. Chattaway

704. Antibacterial Activity *in vitro* of Fucidin

M. BARBER and P. M. WATERWORTH. *Lancet* [Lancet] 1, 931-932, May 5, 1962. 3 refs.

At the Postgraduate Medical School, London, the bactericidal action of "fucidin" was tested against *Staphylococcus aureus*. In tests with a small inoculum, giving approximately 5,000 staphylococci per ml., fucidin in a concentration of 0.5 µg. per ml. killed 90% of the cells in 15 hours and practically sterilized the culture in 24 hours. With a larger inoculum to give 3 million cells per ml., a concentration of 0.5 µg. per ml. also killed 90% in 15 hours, but the few surviving cells subsequently multiplied, so that by 30 hours visible growth had occurred. These organisms were shown to have an increased resistance to fucidin. Fucidin exerted a synergistic action with penicillin against penicillinase-producing strains of *Staph. aureus*. In further studies the authors found that cephalosporin P₁ had properties very similar to those of fucidin.

F. W. Chattaway

705. *In-vitro* Studies of a New Antibiotic (Fucidin)

G. R. F. HILSON. *Lancet* [Lancet] 1, 932-933, May 5, 1962. 4 refs.

Working at St. George's Hospital Medical School, London, the author found that "fucidin" has a minimum inhibitory concentration in nutrient agar of 0.1 µg. per ml. or less for 240 strains of *Staphylococcus pyogenes*. The drug was stable in sterile aqueous solution but inactivated in the

presence of the growth of a number of bacteria, probably as a result of the development of an alkaline reaction in the medium. Resistant mutants were isolated.

F. W. Chattaway

706. Antistaphylococcal Activity of Fucidin

G. TAYLOR and K. BLOOR. *Lancet* [Lancet] 1, 935-937, May 5, 1962. 1 ref.

In an investigation at the Royal Infirmary, Manchester, into the antistaphylococcal activity *in vitro* of "fucidin", the minimum inhibitory concentration (M.I.C.) for 100 strains of *Staphylococcus aureus* was found to be between 0.06 and 0.5 µg. per ml. The concentration required to kill the organisms was either twice or 4 times the M.I.C. Tolerance to fucidin proved very easy to induce. Treatment of 8 patients with infections due to *Staph. aureus* showed that the drug was highly active, particularly when used with benzylpenicillin against penicillinase-producing staphylococci. In this limited clinical trial no resistant strains developed and there were no toxic reactions.

F. W. Chattaway

707. Antibacterial Activity of the Penicillins

M. BARBER and P. M. WATERWORTH. *British Medical Journal* [Brit. med. J.] 1, 1159-1164, April 28, 1962. 8 figs., 35 refs.

Penicillin has the disadvantages of relative instability, rapid excretion through the kidney tubules, and possible inactivation by penicillinase-producing organisms. The use of procaine salts, of benzathine penicillin, or of probenecid to block excretion permitted more prolonged action, and now that different side-chains may be attached to the 6-aminopenicillanic acid nucleus, penicillins with many different properties are becoming available. The antibacterial activity of some of these penicillins has been studied at the Postgraduate Medical School of London.

Available penicillins which are resistant to gastric acid include benzathine penicillin, phenoxymethylpenicillin, phenethicillin, propicillin, phenbenicillin, ampicillin, and "prostaphlin", an isoxazolyl penicillin. Methicillin, prostaphlin, and the cephalosporins are resistant to penicillinase. Ampicillin and the cephalosporins are active against Gram-negative bacilli. Tests of bacteriostatic activity showed that phenoxymethylpenicillin is as effective as benzylpenicillin against the sensitive Gram-positive bacteria and *Neisseria gonorrhoeae*, the others being less effective. Against *N. meningitidis* phenoxymethylpenicillin and ampicillin have only one-quarter of the activity of benzylpenicillin. Ampicillin was much more effective than the other penicillins against Gram-negative bacilli. It was also found that 2% to 3% of staphylococcal strains showed naturally-occurring tolerance to penicillinase-resistant penicillins. Strains rendered resistant to passage in the presence of methicillin grew poorly in high concentrations of isoxazolyl penicillins.

In summary, benzylpenicillin is the best against species which are usually sensitive, and ampicillin is the choice against Gram-negative bacilli, being highly active against

Haemophilus influenzae and *Salmonella*. Phenethicillin, propicillin, and phenbenicillin possess inferior antibacterial activity, although the manufacturers claim they are better absorbed and give higher blood levels. It is considered unlikely that drug-resistant strains will arise with the penicillinase-resistant penicillins, but this is possible with wide usage and cross-infection. These penicillins should therefore be reserved for the treatment of severe penicillin-resistant staphylococcal infections and the patients should be isolated.

T. B. Begg

708. Phenethicillin: Laboratory and Clinical Evaluation in Infants and Children

H. D. RILEY JR. *Antibiotics and Chemotherapy* [Antibiot. and Chemother.] 11, 749-757, Dec., 1961 [received March, 1962]. 12 refs.

In a trial at the Children's Memorial Hospital, Oklahoma City, the value of phenethicillin, administered by mouth, was assessed in the treatment of infections in 102 children, of whom 68 had respiratory infections and 34 skin or soft-tissue infections. The majority of cases with streptococcal and pneumococcal infections responded satisfactorily, as did 50% of those with staphylococcal infections. These last were not considered to be due to hospital-acquired strains. Of the 13 staphylococcal strains isolated, 9 were susceptible *in vitro* to phenethicillin and benzylpenicillin, and 4 were resistant to both antibiotics. All strains of β -haemolytic streptococci tested were susceptible to both penicillins. Only one patient had an untoward reaction to phenethicillin. Phenethicillin was not considered to be more effective than benzylpenicillin.

F. W. Chattaway

709. Evaluation of Phenethicillin, an Oral Synthetic Penicillin, in the Treatment of Soft Tissue Infections

A. PRIGOT and B. A. SHIDLOVSKY. *Antibiotics and Chemotherapy* [Antibiot. and Chemother.] 11, 758-763, Dec., 1961 [received March, 1962]. 3 figs., 8 refs.

The value of phenethicillin, in a basic dosage of 250 mg. 4 times per day, in the treatment of 150 cases of soft-tissue infection, was examined at the Harlem Hospital Center, New York. Clinical results were judged to be excellent. There were no side-effects and 10 patients previously found allergic to penicillin tolerated the phenethicillin. Cultures were obtained from 95 cases and all bacteria normally susceptible to penicillin were inhibited by phenethicillin. In 43 cases where a single organism was isolated, susceptibility could be determined by either tube-dilution or disk methods of assay. However, there was no correlation between the size of the zone of inhibition of the disks and the minimum inhibitory concentration found by the tube-dilution method.

F. W. Chattaway

710. Cholestatic Jaundice in Patients Treated with Erythromycin Estolate

W. P. HAVENS JR. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 30-32, April 7, 1962. 3 refs.

In this paper from Jefferson Medical College, Philadelphia, 4 cases of jaundice following treatment with erythromycin estolate ("ilosone") are described. All the patients (3 male and one female, aged 19 to 59 years) gave a history of allergy, the allergens being sulphonamides, penicillin, foods, and pollens; one patient had an allergic skin reaction following a tick bite. The conditions for which erythro-

mycin was given were acne vulgaris, sore throat, cellulitis of the nose, and otitis externa. Except for the female, who had taken unknown amounts of erythromycin, the dosage of this drug was 250 mg. 3 times a day for periods varying from one week to 4 weeks.

The chief symptoms were itching and jaundice and the main clinical features were fever (temperature 100° to 101° F.; 37.8° to 38.3° C.), jaundice, and a palpable liver. The serum bilirubin level ranged from 4.6 mg. per 100 ml. to 28 mg. per 100 ml. and the serum alkaline phosphatase content from 3.6 to 30 Bodansky units. Thymol turbidity (3 cases only) measured 2.1 to 11 units and the response to the cephalin flocculation test (also 3 cases only) was positive in 2 cases and negative in one. The serum glutamic oxalacetic transaminase level, which was determined in 3 cases, ranged from 49 to 1,780 units. The jaundice lasted 2 to 15 weeks, recovery being complete in 3 cases. The female patient still had an enlarged liver 6 months later and a disturbed serum electrophoretic pattern—albumin 3.22 g. per 100 ml., and globulin 3.17 g. per 100 ml., of which 1.52 g. per 100 ml. was found in the gamma fraction.

Prednisone was given to 3 patients in a dosage respectively of 40 mg. daily for 10 days, 40 mg. daily gradually reduced over a period of 3 weeks, and (in the female) 80 mg. daily at first gradually reduced over a period of 7 weeks.

I. M. Librach

SULPHONAMIDES

711. Sulphamethoxazole; Experimental and Clinical Studies of a New Sulphonamide in Children. (Sulfamethoxazol, experimentelle und klinische Untersuchungen eines neuen Sulfonamids beim Kind)

M. RENTSCH. *Deutsche medizinische Wochenschrift* [Dtsch. med. Wschr.] 87, 491-498, March 9, 1962. 13 figs., 5 refs.

From the University Children's Hospital, Berne, the author reports an experimental and clinical study of a new sulphonamide preparation, sulphamethoxazole (3:4-dimethyl-5-sulphanilamido-isoxazol). In preliminary tests on 2 children aged 11 and 13 years respectively, who were given a single dose of 50 mg. per kg. body weight by mouth, the drug was rapidly absorbed, and the peak concentrations in the plasma after 4 hours were 19.1 mg. per 100 ml. for total sulphonamide and 16.7 mg. per 100 ml. for free sulphonamide. Therapeutic concentrations were still present after 12 hours. Somewhat lower concentrations were obtained in an infant aged 11 months, and when the drug was given after a meal absorption was delayed, the maximum value not being obtained until 6 hours after ingestion. Lower values were also obtained in 3 children with the nephrotic syndrome. No accumulation of the drug occurred in 3 children aged 9 to 13 years who received an initial single dose of 50 mg. per kg. body weight followed by a maintenance dose of 20 mg. per kg. every 12 hours and in whom plasma levels varied between 10 and 15 mg. per 100 ml., nor in an infant aged 7 months with renal hypoplasia.

The half-life value of the plasma total sulphonamide level was 7 hours in an infant aged 11 months, 8.2 hours in 2 children aged 9 years, and 9 hours in 2 children aged 12 years. The half-life values for free sulphonamide were 7.2 hours for the infant and 7.8 hours for the other children. After a single oral dose, 65% of total sulphonamide and 35% of free sulphonamide was excreted in the course of 4

days, about half of the drug being excreted in the first 12 hours. The drug was excreted at equal rates in 5 healthy children, in 3 with diabetes, and in one child in the acute phase of the nephrotic syndrome. In 4 children aged 7 to 24 months who were given a single dose of 50 mg. per kg. body weight by mouth, free sulphonamide was found in the cerebrospinal fluid in a concentration of 3.5 mg. per 100 ml. 12 hours later, this being about 60% of the plasma level at that time. In tolerance studies carried out in children aged 7 to 13 years who were given the drug for 6 months no side-effects were noted, apart from leucopenia which was observed in 2 cases.

At the conclusion of these preliminary investigations the drug was given to 7 children with acute pyuria and to 40 with chronic urinary infections, the initial dose being 40 mg. per kg. body weight followed by a maintenance dose of 20 mg. per kg. twice a day. The result was considered to be "very good" (urine completely normal) in 4 of 7 children with acute urinary tract infection and in 14 of 40 with chronic urinary tract infection. A "good" result (no protein and leucocytes fewer than 10 per c.mm. but the urine not sterile) was obtained in 2 and 11 of the children in the above two groups respectively. Two case histories are quoted in illustration.

From the results it is concluded that the drug is well tolerated and is particularly effective against Gram-negative organisms (*Proteus* and *Escherichia coli*). Its use is indicated in acute and chronic infections of the urinary tract, but for the latter, treatment must be continued without interruption for at least 6 months.

Anne Tothill

CHEMOTHERAPY OF TUMOURS

712. Recurrent Cancer of Head and Neck. Treatment with Continuous Intra-arterial Methotrexate and Intermittent Intramuscular Citrovorum Factor

G. WESTBURY, K. A. NEWTON, J. G. HUMBLE, H. T. FORD, D. E. PEGG, and W. F. WHITE. *British Medical Journal* [Brit. med. J.] 1, 1238-1242, May 5, 1962. 5 figs., 4 refs.

This paper from the Westminster Hospital, London, describes the treatment of 26 cases of inoperable cancer of the head and neck, recurrent after previous radiotherapy, by continuous intra-arterial administration of the anti-metabolite methotrexate and the intramuscular injection of citrovorum factor. In most of these cases the external carotid artery was cannulated through the superior thyroidal artery with a polyvinyl chloride catheter, the position of the catheter tip being confirmed by inspection under ultraviolet light after the injection of fluorescein; in a few patients cannulation was through the superior temporal or common carotid artery. The dosage of methotrexate varied up to 50 (occasionally 100) mg. daily to a total of about 150 to 800 mg. given over 5 to 21 days; all the patients also received intramuscularly 6 mg. of citrovorum factor 6-hourly. Side-effects included a mucosal reaction in 6 cases, similar to that caused by radiation, leucopenia in 7 cases, and thrombocytopenia in 4. Staphylococcal infection occurred in 5 patients, of whom one died from secondary haemorrhage after withdrawal of the catheter. Hemiplegia occurred transiently in 2 patients and permanently in one. In addition 2 further patients died, one from massive pulmonary embolus and one from bronchopneumonia after thrombosis.

In this series 21 patients had carcinoma of the lip, cheek, jaw, palate, antrum, or ethmoid, 2 had carcinoma of skin, and there were 2 cases of rhabdomyosarcoma and one of fibrosarcoma. In most cases there had been local recurrence, several having metastases to lymph nodes. Of the 26 cases, 18 showed some objective regression, there being complete regression in 3 at periods varying from 2 to 5 months after infusion; of these 3 patients, however, only one was still alive and well at the time of reporting.

K. E. Halnan

713. Mannitol Busulphan in Disseminated Breast Carcinoma

E. BOESEN. *British Medical Journal* [Brit. med. J.] 1, 1228-1231, May 5, 1962. 3 figs., 7 refs.

From the Royal Free Hospital, London, the author reports on the use of mannitol "busulphan" in the treatment of 11 patients with advanced cancer of the breast; this substance is an alkylating agent and is also known as mannitol myleran or C.B. 2511. In 6 cases 2 to 3 g. of the drug was given intravenously 3 times per week until a fall in the leucocyte count occurred; a further 4 patients received 3 or 4 g. daily for 3 or 4 days, but this resulted in agranulocytosis. One patient was given a single injection of 17 g. intraperitoneally. "Maintenance" treatment in a dosage of 1 to 2 g. weekly was given when the blood count seemed to allow it.

Nausea and vomiting occurred in 3 patients. In all cases there was depression of the leucocyte count; one patient died from agranulocytosis, and alopecia developed in 2. All the patients reported subjective improvement; however, 3 died within 3 months. Objective improvement was claimed by 5 patients, but decrease in the size of tumour deposits was seen in only 3. The author did not find mannitol busulphan to have any advantage over other similar agents.

K. E. Halnan

714. Intraluminal Injection of Nitrogen Mustard as Adjuvant Chemotherapy in Treatment of Cancer of the Colon and Rectum

L. M. ROUSSELOT and D. R. COLE. *Surgery, Gynecology and Obstetrics with International Abstracts of Surgery* [Surg. Gynec. Obstet.] 114, 409-414, April, 1962. 6 figs., 16 refs.

From New York University School of Medicine the authors present an account of a technique for the intraluminal introduction of nitrogen mustard or other cytotoxic drug before performing resection of the colon or rectum for malignancy, the aim being to destroy free-floating cancer cells present in the segment to be resected or in the local mesenteric, venous, and lymphatic drainage of this area at the time of operation. The results in the first 20 patients treated with 0.4 mg. of mustine per kg. body weight are briefly described. The main wound healed by first intention in 18 cases. The method has only recently been tried, so that follow-up studies are not yet available. There were no evidence of bone-marrow depression or other indications of drug toxicity with the dosage employed. The technique is advocated as reducing the risk of recurrence of the tumour.

G. Calcutt

715. Chemotherapy of Malignant Disease: a Review of Theory and Practice

G. D. HART. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 575-583, March 31, 1962. 3 figs., 32 refs.

Infectious Diseases

716. Leptospirosis: a Comparison of Symptomatic and Penicillin Therapy

R. S. KOCEN. *British Medical Journal* [Brit. med. J.] 1, 1181-1183, April 28, 1962. 13 refs.

The different results obtained with various antibiotics in the treatment of leptospirosis in human beings emphasize the difficulty of judging the therapeutic efficacy of these drugs in clinical trials. A comparative study is reported from the British Military Hospital, Taiping, Malaya, of the course of leptospirosis in 28 patients treated with penicillin and the course in 33 patients treated symptomatically. Penicillin was found to reduce the duration of pyrexia in cases treated within 4 days of the onset as well as in those treated later. It also possibly reduced the incidence of jaundice, renal involvement, and neck stiffness, apparently by preventing these symptoms from developing after more than 48 hours from the onset of treatment. It is concluded that, while sufficient evidence exists for the use of penicillin in the treatment of this disease, further investigations are warranted, but these should be conducted only by doctors who are aware of the possibility of leptospirosis being a cause of pyrexia in patients without the classic symptoms of Weil's disease.

Edward Hindle

717. Fungus Infections in Leprosy Patients. (Микозы у больных лепрой)

V. G. ANDREEV. *Вестник Дерматологии и Венерологии* [Vestn. Derm. Vener.] 36, 15-20, April, 1962. 8 refs.

A study of the incidence of fungus infections, diagnosed on the basis of clinical and laboratory findings, showed that of 653 patients with leprosy 33.1% also had fungus infections. In a control group of 300 patients attending the skin clinic for other disorders the incidence of fungus infections was found to be only 7.7%. The incidence of the various types of fungus infection is presented in a table. The author concludes that there may be some symbiosis between various fungi and the *Mycobacterium leprae*.

N. Hopewell

718. Histoplasmosis Involving the Heart and Great Vessels

G. E. OWEN, S. N. SCHERR, and E. J. SEGRE. *American Journal of Medicine* [Amer. J. Med.] 32, 552-559, April, 1962. 5 figs., 19 refs.

By means of surveys in which the histoplasmin skin test was used, it has been estimated that some 30 million Americans have a symptomless infection with *Histoplasma capsulatum*. This paper, from the State University of New York and the Veterans Administration Hospital, Syracuse, New York, reports 4 cases of acute histoplasmosis involving the heart and great vessels. In the first patient the chief feature was pericarditis with effusion. The other 3 patients had hilar and parenchymatous masses, in one causing auricular flutter with a 2:1 block and in 2 obstruction of the superior vena cava. The criteria for diagnosis were the clinical and histological features and the result of the histoplasmin skin test, which was positive in all 4 cases. In 3 of the patients the histoplasma complement fixation test was positive; in one of these, intrahistiocytic bodies suggestive of *H. capsulatum*

were seen on histological examination of a granulomatous mass. One patient was treated with *p*-aminosalicylic acid and isoniazid and another with amphotericin B.

Winston Turner

VIRAL DISEASES

719. Epidemiological and Prophylactic Aspects of a Recent Epidemic of Poliomyelitis. (Les aspects épidémiologiques et prophylactiques d'une épidémie récente de poliomyélite)

P. MELNOTTE and F. MOTTON. *Bulletin de l'Académie nationale de médecine* [Bull. Acad. nat. Méd. (Paris)] 146, 291-299, April [received June], 1962. 1 fig.

This report from the Public Health Office of the Aube department, Troyes, France, describes how an epidemic of poliomyelitis was checked by a vigorous vaccination campaign. From 1945 to 1960 inclusive the annual number of cases of poliomyelitis in the Aube department, which has a population of 250,000, was never more than 25. In 1961, however, there were 119 cases, most of which occurred in an epidemic caused by Type 1 poliomyelitis virus. The incidence of the disease in 1961 was low until the end of May (19 cases from January to May inclusive), and the epidemic was concentrated in the months of May, June, and July (91 cases), after which the monthly incidence returned to the normal level and remained at that level for the last 5 months of the year (9 cases). Meanwhile, in the rest of France the incidence continued to rise, reaching its maximum in October and then slowly declining. The position as regards vaccination in the Aube department was that between 1958 and the end of May, 1961, 8,034 subjects (31% of the population aged less than 20 years) had been vaccinated with the Pasteur Institute vaccine. When the epidemic began the number of vaccination centres was increased and some 30,000 complete courses and 6,138 booster doses were given, the percentage of those under 20 who had received protection thus being brought to nearly 100. It was considered that this high protection rate was responsible for the abrupt fall in case incidence in the late summer, when, in view of the hot, dry weather, the epidemic would otherwise have been expected to continue. None of the children vaccinated contracted the disease.

J. E. M. Whitehead

720. The Pathogenetic Importance of Vascular Lesions in Poliomyelitis. (Interesse patogenetico della compromissione vascolare nella poliomielite)

G. C. ANGELA and G. GIULIANI. *Minerva medica* [Minerva med.] 53, 767-771, March 14, 1962. 8 figs., 15 refs.

From the results of experimental investigations carried out on monkeys at the Institute of Virology, Turin, and of histological examination of patients who died of poliomyelitis, the authors conclude that in this disease vascular lesions precede the viral lesions in the neurones. The changes in the capillary wall seem to be responsible for the invasion of the nerve cells by the virus by permitting passage of the latter from the blood. These vascular lesions and oedematous swellings either reduce or interrupt the flow of

blood and so lead to hypoxia, with resulting impairment of the function of the neurones, the degree of injury to the nerve cells being related to the duration of the hypoxia. The recovery of the neurones affected by hypoxia alone requires an adequate blood supply. It is therefore essential that cortisone or one of its derivatives should be administered early so as to reduce the infiltration of the blood vessels.

Franz Heimann

721. The Virus of Venezuelan Equine Encephalomyelitis as an Antineoplastic Agent in Man

W. D. TIGERTT, W. H. CROSBY, T. O. BERGE, D. L. HOWIE, S. KRESS, H. G. DANGERFIELD, J. W. BASS, and W. FRANK. *Cancer [Cancer (Philad.)]* 15, 628-632, May-June, 1962. 13 refs.

This paper from the Walter Reed Army Medical Center, Washington, describes the effect of inoculating an attenuated strain of Venezuelan equine encephalomyelitis in 8 adult volunteers with histologically proven lymphomata. Four of the patients were considered to have pre-terminal cancer (3 cases of Hodgkin's disease and one of reticulum-cell sarcoma) and 4 to have less advanced cancer (3 cases of lymphosarcoma and one of Hodgkin's disease). The 4 patients with pre-terminal cancer died within 5 weeks of virus inoculation, only one of them showing unequivocal clinical evidence of a viral infection. In all the 4 less advanced cases there was clinical or radiological evidence of regression of tumour masses, and obvious subjective improvement occurred in 3. The improvement was preceded by a febrile illness with temporary suppression of circulating leucocytes and blood platelets. There was no clinical or histological evidence of encephalitis in the pre-terminal patients' and overt clinical encephalitis did not occur in the others. The authors consider that the temporary tumour regression obtained, and the absence of encephalitis, suggest that this method might also be tried in less advanced cases.

D. Geraint James

722. Herpes Zoster Encephalitis

E. APPELBAUM, S. I. KREPS, and A. SUNSHINE. *American Journal of Medicine [Amer. J. Med.]* 32, 25-31, Jan., 1962. 2 figs., 34 refs.

A study is reported of 14 cases of encephalitis associated with herpes zoster, 11 of which were seen in the New York City Department of Health between 1932 and 1960. [Since this is a rare form of encephalitis such a comprehensive report is a considerable contribution to our knowledge, but unfortunately it casts no new light on the pathogenesis of the disease.] There were no deaths in the series and therefore no opportunity to study the pathological changes in the brain and spinal cord.

It is pointed out that herpes zoster mainly affects the middle-aged and elderly. Only 4 of the 14 patients were under 40 years of age; the remainder were aged 40 to 87 years. In most cases signs of encephalitis were noted a few days after the appearance of the rash, but in 4 cases they preceded the eruption by a few days and in one case by 3 weeks. The mode of onset was usually acute with moderate fever and meningeal signs predominating, but in 3 cases the onset was gradual. Cerebellar signs were noted in one case only. [This is of interest since varicellar encephalitis, a closely allied condition, is not infrequently of the cerebellar type.] Cerebrospinal-fluid examination revealed pleocytosis

(35 to 140 cells per c.mm., predominantly lymphocytes), a moderate increase in the protein concentration, a normal sugar level, and a chloride content which was on the low side. Colloidal gold tests were carried out in 4 cases, and in 2 of these a first-zone curve was obtained. In these 2 cases also the electroencephalogram was abnormal. At follow-up examination of 9 of the patients 3 had residual neurological sequelae, including the 2 showing an abnormal response to the colloidal gold test and an abnormal electroencephalogram.

The authors note [with surprising emphasis] the occurrence of a varicelliform eruption in 4 patients in the series. [This is not an unusual finding in middle-aged patients with herpes zoster.] Treatment was mainly symptomatic, but attention is drawn to the suppressive effect of steroids in experimental demyelinating encephalitis and the possible favourable influence of these drugs in measles encephalitis.

H. Stanley Banks

723. Clinical, Epidemiological, and Virological Aspects of Echovirus Type 9 Infection in Sheffield, 1960

D. HOBSON, J. M. HOSKINS, J. HORNER, A. H. CLARKE, and F. B. G. WOOD. *British Journal of Preventive and Social Medicine [Brit. J. prev. soc. Med.]* 16, 84-92, April, 1962. 2 figs., 14 refs.

This paper from the University of Sheffield describes an epidemic of aseptic meningitis due to E.C.H.O. virus Type 9 which occurred in that city in the summer of 1960. The clinical picture was non-specific; the cerebrospinal-fluid pressure was slightly raised, and examination of the fluid showed the presence of 100 to 5,000 cells per c.mm., the majority of them lymphocytes, a raised protein content, but no change in concentration of chloride or sugar. Of the 47 patients with aseptic meningitis investigated, E.C.H.O. virus Type 9 was isolated from 12, 11 of whom were under 16. Another clinical manifestation of infection with this agent appeared in the Sheffield district at the same period. This was a rubelliform rash, occurring in children (usually under 4 years) and often associated with constitutional disturbance, diarrhoea, vomiting, pharyngitis, and occipital or cervical lymphadenopathy. Of 57 such cases investigated, E.C.H.O. virus Type 9 was recovered in 22. Little overlap between the two forms of clinical disease was apparent. Virus strains isolated from patients with meningitis and from patients with rubelliform rash or from apparently healthy children appeared to show little difference in laboratory behaviour. There was little evidence of immunization by previous virus exposure in the normal general population. The possibility that many adult illnesses may be derived from a reservoir of infection in small children, and the possible role of host factors in the infectivity and virulence of E.C.H.O. virus Type 9, are discussed. D. Geraint James

724. Immunity to the Common Cold from Protective Serum Antibody: Time of Appearance, Persistence and Relation to Reinfection

G. G. JACKSON, H. F. DOWLING, L. W. AKERS, R. L. MULDON, A. VAN DYKE, and G. C. JOHNSON. *New England Journal of Medicine [New Engl. J. Med.]* 266, 791-796, April 19, 1962. 6 figs., 9 refs.

In continuance of their previous work, in which they demonstrated the capacity of agents of the common cold to stimulate an antibody response in man, the authors, in this

paper from the University of Illinois, Chicago, describe controlled experiments to determine the rate of development and the persistence of (a) neutralizing antibody against an infectious common cold secretion, and (b) immunity to infection upon rechallenge with the same secretion.

Two antigenically identical nasal secretions obtained from donors with naturally acquired common colds, and a nasal secretion collected from a volunteer who had been infected with one of these natural secretions, were tested. The effectiveness with which convalescent-phase serum, collected one, 6, 12, 18, and 24 months after induction of the experimental cold, neutralized the infectivity of the homologous common cold secretion was tested by challenging volunteers with the secretion incubated with the convalescent serum. Both illness rate and daily symptom scores were compared with those of controls. The results showed that convalescent sera collected one month after the initial infection conferred only slight protection against the infectious secretion, those collected at 6 and 12 months provided almost complete protection, while those collected at 24 months gave little or no protection. The immunity of volunteers to infection upon rechallenge with the same infectious secretion was observed. The results resembled very closely those noted for the development of serum neutralizing antibody.

It is concluded that if these results can be regarded as representative, then "neither clinical infection nor live-virus vaccines could be expected to give a lasting immunity".

Kurt Schwarz

725. Anicteric Hepatitis: Studies of Four Epidemics
L. M. MORRISON, R. E. HOYT, M. ROSENTHAL, M. G. LEVINE, and R. HOLEMAN. *Archives of Environmental Health [Arch. environm. Hlth]* 4, 538-546, May, 1962. 2 figs., 21 refs.

Estimates of the frequency of anicteric forms of hepatitis have been rising since the observations made in the Middle East in the second world war. The authors of the present paper, in a series of reports since 1957, estimated this frequency at 70% to 80% of all cases of viral hepatitis. In the view of Stokes (*J. Amer. med. Ass.*, 1960, 172, 652) and others, one case, and possibly 2, of hepatitis without jaundice could be found for every case of infective hepatitis with jaundice. The authors have now studied 4 further epidemics, and conclude that under some circumstances the incidence of anicteric hepatitis may rise to equal or exceed that of the jaundiced forms. How, then, can anicteric hepatitis be recognized? The main criteria will be applicable particularly in an epidemic setting and will include a characteristic clinical picture, but without jaundice; a palpable, enlarged, or tender liver; the presence of haemagglutinins for viral hepatitis; positive thymol turbidity and cephalin-cholesterol flocculation tests; normal serum bilirubin level; and a negative heterophil antibody test to rule out infectious mononucleosis. Such findings indicate a trend towards hepatic impairment in anicteric viral hepatitis, and also suggest a relationship with non-alcoholic cirrhosis of the liver, some evidence for which is given.

This form of hepatitis is apt to be missed; it should be looked for especially in the families and others in direct contact with a jaundiced patient. An effective preventive measure for contacts in an epidemic is the injection of γ -globulin in a dose of 0.02 ml. per lb. (0.044 ml. per kg.) body weight. [Incidentally the haemagglutinins found in viral hepatitis have been shown to be γ -globulins.] Treatment

of anicteric hepatitis is similar to that of the jaundiced form; it includes a nutritious diet, rest, vitamin supplements, and corticosteroid therapy for persistent cases with chronic symptoms or impaired liver function, persistently tender liver, severe fatigue, and depressive psychiatric symptoms.

H. Stanley Banks

726. Infectious Hepatitis. Report of an Outbreak in a Small Connecticut School, Due to Water-borne Transmission
M. E. RINDGE, J. O. MASON, and W. R. ELSEA. *Journal of the American Medical Association [J. Amer. med. Ass.]* 180, 33-37, April 7, 1962. 2 figs., 13 refs.

A survey by Mosley in 1959 revealed only 28 known epidemics of hepatitis attributed to water-borne infection; of these only 3 were school outbreaks. Another school outbreak is now reported (from the Connecticut State Department of Health, Hartford, and the Public Health Service, Department of Health, Education, and Welfare, Washington) among a group of children who usually drank from one of the two school wells which was shown to be subject to fairly heavy faecal contamination. This outbreak, comprising some 30 cases, occurred in July and August, 1960, and was explosive in character. Food, milk, school buses, and social gatherings could all be ruled out as sources of infection, and the only determined source that was common to all the cases was the water supply on the west side of the school. None of the pupils who usually drank from the well on the east side of the school was affected.

The onset of symptoms in 20 of the patients occurred during a 23-day period in July; this is shorter than the usual incubation period of infective hepatitis and suggests a common source of infection in all 20 cases; a further 9 cases occurred in August, and in all of these there was a history of contact with cases in the first wave. Coliform organisms were found in 8 of 14 samples from the west well and in one of 13 samples from the east well. There was a preponderance of males among the patients, a feature also observed in the majority of previously reported water-borne outbreaks.

H. Stanley Banks

727. Transaminase Activity of the Serum in Infectious Mononucleosis. (Il comportamento dell'attività transaminasica del siero nella mononucleosi infettiva)

L. ROBERT and C. E. GROSSI. *Archivio E. Maragliano di patologia e clinica [Arch. E. Maragliano Pat. Clin.]* 18, 267-275, April, 1962. 2 figs., bibliography.

The concentration of serum glutamic-oxalacetic transaminase (S.G.O.T.) and of serum glutamic-pyruvic transaminase (S.G.P.T.), and the S.G.O.T.:S.G.P.T. ratio, were investigated in 10 patients suffering from infectious mononucleosis at the Ospedali Civili, Genoa. The S.G.P.T. and the S.G.O.T. values were both found to be above normal, the increase in the former being greater than that in the latter, with consequent inversion of the S.G.O.T.:S.G.P.T. ratio. The increase was maximal during the first week of the infection, and did not exceed 300 Karmen units (S.G.O.T.) or 300 Wróblewski units (S.G.P.T.). No correlation was found between the level of the serum transaminases and the severity of the clinical symptoms. The authors conclude that the liver parenchyma is damaged in all cases of infectious mononucleosis, but that generally the damage is not accompanied by icterus. Investigation of the serum

transaminase level is a useful aid to diagnosis of this disease, provided it is performed early (within the first week). Similarities between infectious mononucleosis and viral hepatitis are pointed out (liver damage, generally without icterus; similar changes in serum transaminase level).

Other work on the subject is reviewed.

Franz Helmann

[For definition of the units mentioned above the reader is referred to the *Lancet*, 1959, 1, 256.—EDITOR.]

lin. The part played by benzylpenicillin in such combined action would seem to be explained by the ability of the other member of the drug pair to interfere with the production of penicillinase. While it may be hoped that the methicillin type of drug will solve many of the problems in the management of antibiotic-resistant staphylococcal infections, "the possibility must be considered that combined therapy may again become necessary... because of the remarkable adaptability of staphylococci".

H. Stanley Banks

BACTERIAL DISEASES

728. Staphylococcal Endocarditis: Results of Combined Antibiotic Therapy in Fourteen Consecutive Cases (1956-1959)

E. JAWETZ and H. D. BRAINERD. *American Journal of Medicine* [Amer. J. Med.] 32, 17-24, Jan., 1962. 1 fig., 11 refs.

Since 1953 one of the authors and his colleagues have stimulated much thought and research on the difficult subject of synergism and antagonism in antibiotic combinations. In the present paper a study is reported of the results of treatment in 14 cases of staphylococcal endocarditis (9 of which were penicillin-resistant) seen among a total of 50,687 patients admitted to the California Medical Center, San Francisco, in the period 1956 to 1959 inclusive. The patients were treated with proved bactericidal combinations, determined by the results of tests *in vitro* on the organism with each antibiotic, both singly and in various combinations of pairs of the drugs. The inhibition level of each drug against the staphylococcus isolated was first determined in $\mu\text{g. per ml.}$, and then various pairs of the drugs were tested against the organism for their bactericidal activity. Suitable bactericidal pairs of the following drugs were selected for administration—penicillin, bacitracin, streptomycin, chloramphenicol, tetracycline, erythromycin, neomycin, kanamycin, and novobiocin. Of the 12 patients so treated 10 were cured, although the organisms in 8 of them were completely penicillin-resistant, growing freely in benzylpenicillin ($6 \mu\text{g. per ml.}$). [Since untreated staphylococcal endocarditis is invariably fatal, either from overwhelming toxæmia or from tissue destruction and ultimate congestive heart failure, this result must be regarded as both a therapeutic achievement and a scientific advance.] The onset of endocarditis followed cardiac surgery in 3 patients and self-induced abortion in one; in 3 further patients it was associated with corticosteroid therapy.

The authors point out that the purpose of this report was not to discuss the clinical features of staphylococcal endocarditis but rather "to use this disease as a model" for the evaluation of bactericidal pairs of drugs in the treatment of serious penicillin-resistant staphylococcal infections. The study was carried out before the introduction of the penicillinase-resistant drug, methicillin. However, the results *in vitro* with the pairs of drugs found to be bactericidal were compared with the results *in vitro* with methicillin, 6 of the penicillin-resistant strains of staphylococci isolated being tested; all these were killed by methicillin in a concentration of $6 \mu\text{g. per ml.}$ For the present, therefore, this valuable work must be considered to be superseded by the discovery of methicillin, which appears to have effects indistinguishable from those of some drug pairs containing benzylpenicil-

729. The Use of Antistaphylococcal Serum during Treatment with Antidiphtheritic Serum. (Sull'uso del siero antistafilococcico in corso di trattamento con siero antidifterico) C. PANERO. *Rivista di clinica pediatrica* [Riv. Clin. pediat.] 68, 316-323, Nov., 1961 [received June, 1962]. 28 refs.

Starting from the premise that pyogenic staphylococci are often associated with diphtheria bacilli and that their toxin contributes to the severity and sometimes fatal issue of diphtheria in children, the author, at the Paediatric Clinic of the University of Florence, added staphylococcal antitoxic serum combined with antibiotics (usually erythromycin) to the conventional treatment with diphtheria antitoxin. The average daily dose of diphtheria antitoxin was 5,000 to 10,000 i.u. per kg. body weight, administered in divided doses, alternately intravenously and intramuscularly, for 3 to 7 days. Staphylococcus antitoxin was given once daily in a dose of 5,000 to 10,000 i.u. intravenously together with the intravenous dose of diphtheria antitoxin. The staphylococcus antitoxin was not begun until at least 12 hours after the diphtheria antitoxin. A table gives details of 34 children thus treated during a period of 2 years; 9 cases are described as severe, the others as moderately severe. [No mild cases are included.] The ages of the patients ranged from 9 months to 13 years. Pseudomembranous tonsillitis or pharyngitis was present in 32 cases, complicated in 3 cases by rhinitis, in 2 cases by myocarditis, and in one case by pyoderma. There were 2 cases of laryngitis, of which one was complicated by bronchopneumonia and the other required tracheotomy. In only 20 of the 34 patients was culture for *Corynebacterium diphtheriae* positive; in 5 it was doubtful and in 9 negative. Staphylococci were absent in only 2 cases, in both of which cultures were positive for *C. diphtheriae*. That there were no deaths in the series is attributed in part to the staphylococcus antitoxin.

K. Zinnemann

730. Treatment of Bacillary Dysentery: with Special Reference to Stosstherapy with Tetracycline

D. J. STOKER. *British Medical Journal* [Brit. med. J.] 1, 1179-1181, April 28, 1962. 16 refs.

The author reports from a Royal Air Force Hospital in Cyprus an investigation which aimed: (1) at comparing the effectiveness, in the treatment of bacillary dysentery, of streptomycin given orally with and without sulphonamides; and (2) at ascertaining whether the period in hospital could be reduced by means of "stosstherapy"—that is, the administration of a single massive dose.

Treatment with a mixture of streptomycin and soluble sulphonamide carried out over a period of 5 days resulted in a cure rate of 97%. This result was an improvement on that produced by a mixture of streptomycin and poorly soluble sulphonamide, and significantly better than that achieved with streptomycin alone in twice the dosage. The

results of stosstherapy, in which 2.5 g. of tetracycline was administered in a single dose, were as good as those achieved with streptomycin and sulphadimidine in combination. In addition, however, stosstherapy reduced the duration of treatment by 4 days in every case, thus representing a considerable saving of time and money. The author points out that the rationale of stosstherapy in infection is dependent on achieving a very high and rapid concentration of the therapeutic agent in the blood and so producing wholesale destruction of the invading organism. In the treatment of intestinal infections there is also the continuing local effect of the agent while it is still in the bowel. Tetracycline was used for stosstherapy in the present investigation because streptomycin is not absorbed in any appreciable amount from the gastro-intestinal tract. The mean period spent in hospital by patients treated with the streptomycin and sulphadimidine mixture was 13 days, whereas for those treated with tetracycline stosstherapy it was only 9 days. In the latter the shorter duration of treatment makes the occurrence of complications due to tetracycline unlikely; no complications occurred in the present series.

The author notes that although the basic cost of tetracycline therapy (2.5 g.) is twice that of 5 days' treatment with streptomycin and sulphadimidine, this is more than offset by the saving in working time and hospital costs.

R. G. Meyer

PROTOZOAL DISEASES

731. **The Epidemiology of Toxoplasmosis.** (Epidémiologie de la toxoplasmosse) G. DESMONTS. *Revue d'hygiène et de médecine sociale [Rev. Hyg. Méd. soc.]* 10, 201-217, April-May, 1962. 2 figs., bibliography.

This is a study, from the Toxoplasmosis Research Laboratory, Hôpital Saint-Vincent-de-Paul, Paris, of the incidence of toxoplasmosis in animals and man, of the course of the disease, and of its transmission. In animals, as in man, infection is common but illness rare. The author found contamination in 4% of oxen, 9% of horses, and 72% of sheep, but the parasite is present in most warm-blooded animals. In humans, 85% of adults give positive reactions to blood tests. The incidence of positive reactions rises from the age of one year to reach a maximum at 30 years, with peaks at the ages of 2 to 3 and 15 to 29 years. The disease occurs in all countries, but is most frequent in those with a tropical climate.

Immediately after infection the vegetative forms can be found in the blood, the milk, the saliva, the urine, and throughout the body. As antibodies develop the organism becomes encysted, and the vegetative forms survive only in the brain and perhaps the retina. Both vegetative and encysted forms die rapidly outside the body, but will persist in carcasses and blood. The vegetative forms (but not the cysts) are destroyed by a temperature of 40° C., and by gastric juice. Though infection by the vegetative forms through the mucous membranes or through skin abrasions has occurred, the author believes that ingestion of the cysts in meat is the common route. He cites as evidence the rarity of infection in young children (apart from congenital cases) before the age at which meat is introduced in the diet. A 30% incidence of fresh infection was demonstrated in one hospital where the children received uncooked meat twice a

week. There must, however, also be other modes of transmission, since the disease has been observed in strict vegetarians.

No case of a woman having two affected children, other than twins, has been established. In the author's view, the presence of antibodies before pregnancy precludes infection of the child, and the congenital form of the disease can occur only when a woman contracts the infection while pregnant. He concludes with the advice that parents be encouraged to give their daughters underdone mutton, an inoffensive way of infecting them with toxoplasmosis and thus protecting their future children from the congenital form of the disease.

H. G. Farquhar

732. **Myocardial Parasites: a Report of Two Cases of Probable Toxoplasma Infection**

J. D. REID. *New Zealand Medical Journal [N.Z. med. J.]* 61, 9-12, Jan., 1962. 2 figs., 12 refs.

In view of reports of the finding of *Toxoplasma cruzi* in the heart muscle and of the suggestion of Paulley *et al.* (*Lancet*, 1954, 2, 624; *Abstr. Wild Med.*, 1955, 17, 116) that *T. gondii* might be responsible for cases of myocarditis of obscure aetiology, the author, at Wellington Hospital, New Zealand, has reviewed pathological material from 5 such cases and found what was presumably *T. gondii* in the heart of one of them. This patient was an English seaman who was admitted to hospital after a "turn" had caused him to fall in the street. Five years later he died of heart failure following bouts of arrhythmia and tachycardia. The second case was discovered incidentally in a young woman who died of poliоencephalomyelitis; in this patient *T. gondii* were found in the right ventricle.

Clement C. Chesterman

733. **Some Observations on Laboratory Tests for Toxoplasmosis**

J. D. MANNING and R. E. ALLEN. *New Zealand Medical Journal [N.Z. med. J.]* 61, 12-15, Jan., 1962. 1 fig., 8 refs.

In this paper from the National Health Institute, Wellington, New Zealand, the various laboratory tests for the diagnosis of toxoplasmosis are discussed. The authors then describe a technique by which the diagnosis can be confirmed. In mice inoculated with *Toxoplasma* and which eventually show a positive result in the serum dye test, confirmation is assured by examination of an unstained "squash" preparation of the brain, in which the cysts, though often scanty, are readily recognizable.

Clement C. Chesterman

734. **Congenital Toxoplasmosis: Reports of Two Cases**

H. J. WESTON and R. T. BUSH. *New Zealand Medical Journal [N.Z. med. J.]* 61, 15-18, Jan., 1962. 4 figs., 10 refs.

From the Hutt Hospital, Wellington, New Zealand, the authors report 2 cases of congenital toxoplasmosis in infants aged 6 weeks and 4 months respectively when first seen. The first was a typical case in which there was hydrocephalus due to stenosis of the aqueduct and also chorioretinitis. The other baby showed microcephaly and enophthalmos. No treatment of this condition is of any use, since irreparable damage has probably already occurred *in utero*. The only hope is to diagnose and treat the disease in expectant mothers, but unfortunately in them it is generally symptomless.

Clement C. Chesterman

735. Lymphadenopathy in Toxoplasmosis

J. D. MCCREANOR. *New Zealand Medical Journal* [N.Z. med. J.] 61, 18-20, Jan., 1962. 6 refs.

The author reports the successful treatment of a case of acquired toxoplasmosis in a girl aged 17 who developed slightly tender discrete swellings of the lymph nodes in the posterior triangle of the neck, accompanied by lassitude and night sweats. The serum complement fixation test and the dye test were positive for toxoplasmosis. In hospital a lymph node was removed from the neck and from this mice were subsequently infected. The usual treatment with pyrimethamine and a sulphonamide was effective. The clinical picture in this case is fully discussed.

Clement C. Chesterman

736. Acute Toxoplasmosis with Involvement of the Heart

J. L. ADAMS. *New Zealand Medical Journal* [N.Z. med. J.] 61, 20-24, Jan., 1962. 5 figs., 10 refs.

A case of acute toxoplasmosis with involvement of the heart is described from Wellington Hospital, New Zealand. It occurred in a boy aged 15 who was admitted with a provisional diagnosis of rheumatic fever, with tiredness and night sweats. The lower cervical lymph nodes were palpable and slightly tender and there was a palpable but not tender lymph node in the left axilla. From one of these nodes *Toxoplasma gondii* was isolated by serial passage in mice, thus confirming the diagnosis. The electrocardiographic findings in this case are discussed and illustrated.

Clement C. Chesterman

737. Current Concepts of Congenital Toxoplasmosis. (Aspects actuels de la toxoplasmose congénitale)

J. COUVREUR. *Revue d'hygiène et de médecine sociale* [Rev. Hyg. Méd. soc.] 10, 187-200, April-May, 1962. 32 refs.

This is a review of 227 cases of congenital toxoplasmosis in which the serology was investigated and the clinical records were analysed at the Toxoplasmosis Research Laboratory, Hôpital Saint-Vincent-de-Paul, Paris.

The author estimates (from routine serological tests) that the incidence of the disease in France is 1 to 2 per 1,000 births. There are 4 main presenting features: abnormalities in the size of the skull, convulsions and other neurological manifestations including mental retardation, intracranial calcification, and eye disorders with chorioretinitis. Mono-symptomatic presentation is probably common, and isolated chorioretinitis is perhaps the commonest manifestation of all. Isolated neonatal jaundice, either of brief duration or going on to cirrhosis, may be the only feature. A picture similar to hydrops foetalis and neonatal thrombocytopenia with haemorrhagic features can occur. In 121 cases of isolated hydrocephalus 5 (4.13%) were shown to be due to this disease. On the other hand, infants with serological evidence of the disease may develop normally and show no other signs of it.

The author emphasizes that the disease may flare up at any age, as shown by the presence of both healed and active chorioretinitis in the same child. Serological tests after infancy are not helpful, because they will be only faintly positive, as in 85% of the normal population, but the antibody titre in the aqueous humour is higher than in the serum.

An infant is unlikely to be affected if the mother's disease occurs in the first 3 months of pregnancy, the 4th and 5th

months of pregnancy being the most dangerous. Some 15% of French women reaching reproductive age have no serological evidence of the disease and are therefore susceptible. Expectant mothers should not eat uncooked or insufficiently cooked meat.

In view of the high incidence of this disease and the relative rarity of congenital syphilis, routine testing for the latter would seem to be less justifiable than for congenital toxoplasmosis.

H. G. Farquhar

738. Laboratory Methods for the Diagnosis of Toxoplasmosis in Human Subjects. (Les méthodes de laboratoire appliquées au diagnostic de la toxoplasmose humaine)

J. P. GARIN. *Revue d'hygiène et de médecine sociale* [Rev. Hyg. Méd. soc.] 10, 218-248, April-May, 1962. Bibliography.

The three laboratory methods applicable to the diagnosis of human toxoplasmosis—namely, (1) isolation of the organism, (2) specific serological tests, and (3) non-specific tests which may raise suspicion of the infection—are discussed in this paper from the University of Lyons.

The organism has been identified in smears from blood, bone marrow, skin lesions, and saliva, and from the conjunctival, buccal, tonsillar, or vaginal mucosa, in the cerebrospinal fluid, in the anterior chamber of the eye, and in biopsy material from muscle, lymph nodes, brain, and skin. It is found more frequently post mortem (when it can be identified in most organs) than in the living subject. Confusion with other parasites is possible. If direct staining is not effective, material can be injected (generally the intraperitoneal route is used) into white mice that have been shown to be free from the infection, and the organism identified by examination of ascitic fluid or in the brain post mortem. Passage through other animals may aid identification. Serological evidence is less reliable than discovery of the parasite as proof of infection of test animals.

The complement fixation test and the dye test of Sabin and Feldman (the latter being the most specific test known) are described in detail and sources of unreliability analysed. It has been held that the dye test becomes positive earlier than the complement fixation test and remains positive for a longer period. This has been taken to mean that two different antibodies are involved in the two tests. However, modification of the technique has shown that the antibodies do in fact appear at the same time in both tests, which consequently are positive at the same time. This suggests that the antibodies concerned are the same. The neutralization test of Sabin and Olitsky is mentioned only to be condemned as unreliable. The skin test of Frenkel, used in a similar manner to a Mantoux test, is considered of value in mass surveys, and probably 2 consecutive negative results exclude the disease.

A mild leucocytosis with an increase in mononuclear cells is to be expected when the disease is active, and an eosinophilia of around 10% when antibodies are developing. The erythrocyte sedimentation rate may be raised, and serum electrophoresis reveals a mild increase in the γ -globulin fraction.

The application of these tests and their interpretation in the various clinical forms of the disease are discussed. The author stresses the difficulty of distinguishing recent disease from reactivation of the congenital form. All information, both laboratory and clinical, must be considered before a diagnosis is made.

H. G. Farquhar

Tuberculosis

739. The Tuberculosis Situation in an Area of Tanganyika, following a Five Year Period of Prevention and Treatment C. G. I. GORDON. *Tubercle [Tubercle (Lond.)]* 43, 43-54, March [received May], 1962. 4 figs., 7 refs.

A system of prevention and treatment of tuberculosis has been built up in the Northern Province of Tanganyika, despite limited staff and facilities. This paper from the Ministry of Health Tuberculosis Hospital, Kibongoto, Tanganyika, describes the effect of these measures in different parts of the area in the 5-year period 1957-61. The methods have been described in a previous paper (*Tubercle (Lond.)*, 1961, 42, 148).

Of 1,232 consecutive patients treated at home, 46.5% had been discharged as apparently cured; 36.9% were on active treatment; 8.7% had been lost sight of; 1.2% were repatriated with hopelessly extensive disease; 2.2% had died, just under half from causes other than tuberculosis. Patients dying during the initial period of hospital treatment have been excluded. From 1960 treatment has consisted of "thiazina with indicator" tablets given twice daily, equivalent to a total daily dosage of 300 mg. isoniazid and 200 mg. thiacezone. This has proved as effective as isoniazid with PAS. A total of 130,000 B.C.G. vaccinations, including revaccinations, of non-contacts were carried out.

The results were analysed with reference to selected tribal areas, the characteristics of each tribe being discussed. In the case of the progressive Chagga tribe (some 239,215 persons) 1,575 new cases received treatment, 755 being sputum-smear positive. Among contacts 336 cases of active disease were found, 77 sputum-positive. The proportion of sputum-smear positive cases declined over the years. The more backward Mmeru and Mwarusha tribes (34,425 and 64,319 persons respectively) were not as well covered. In the last 4 years 208 sputum-smear positive cases were admitted and 304 other cases of active disease were also treated. Treatment facilities were even more limited for the primitive nomadic Masai (46,406), who also were not cooperative. The number of sputum-smear positive cases rose from 23 in 1956 to 89 in 1960.

Despite poor living conditions and a low resistance to disease, there is no doubt that effective prevention and treatment in the Chagga area led to a definite reduction in the number of sputum-smear positive cases within 3 years of the introduction of the system and to greater cooperation on the part of the population. Lack of finance and of executive staff are the only factors preventing the progressive control of tuberculosis in African communities.

B. Golberg

740. Hemorrhage in Tuberculosis as an Urgent Indication for Resection of Pulmonary Tissue W. RZEPECKI and P. BADMAJEW. *Diseases of the Chest [Dis. Chest]* 41, 372-377, April, 1962. 21 refs.

The authors briefly discuss the causes of pulmonary or bronchial haemorrhage, and stress that patients die during pulmonary haemorrhage not from loss of blood but from suffocation, due to flooding of the bronchial tree and concomitant spasm of the bronchi. They consider that con-

servative measures are useless in the presence of a patent bleeding artery and point out that a certain analogy exists between pulmonary haemorrhage and the haemorrhage which occurs in peptic ulceration.

At the Sokolowski Sanatorium, Zakopane, Poland, resection was carried out because of severe haemorrhage in 8 tuberculous patients, with "favourable results" in 5. In 2 cases bronchial fistula and empyema developed. The authors believe that their results would have been better if the infecting organisms had been drug-sensitive. In their view such procedures as thoracoplasty and extrapleural pneumothorax are of no value in these cases and better results with resection technique should be obtained in the future. They admit that it is the exception, in resected material, to find the bleeding point; in 7 of their cases only indirect evidence "in the form of blood clots in cavities was obtained".

Paul B. Woolley

741. Characteristics and Prognosis of Pulmonary Tuberculosis in Persons over 50 Years. (Les caractères et le pronostic actuel de la tuberculose pulmonaire chez les sujets âgés de plus de 50 ans)

J. VIDAL, J. J. GUIN, and Y. DÉCOR. *Revue de tuberculose et de pneumologie [Rev. Tuberc. (Paris)]* 26, 1-12, Jan. [received May], 1962.

The authors, working at the University of Montpellier, have been impressed by the curability of tuberculosis in subjects aged over 50. To verify their observations published in 1957, they recently observed 56 women in sanatorium and 99 men in hospital, all aged over 50. Cavitation was present in 91% of the cases and tubercle bacilli were present in the sputum of 87%. Less than 10% of these cases had been detected in routine radiological examination, and failure to carry out such examination in older patients is deplored. Contrary to common opinion, tuberculosis in the majority of patients over 50 is primary. Proof of a previous tuberculous lesion was found in only 13% of the authors' series. Since 3 women and 23 men stopped their treatment prematurely, the results of treatment were assessed on 129 subjects. The treatment (PAS, isoniazid, and streptomycin) did not differ from that given to younger patients. The duration of treatment was less than one year in 44 cases, 12 to 18 months in 42; and more than 18 months in 43. The principal side-effects were digestive intolerance to PAS (31%) and eighth cranial nerve damage due to streptomycin (26%). In assessing the immediate results of treatment the authors claim cure in 81%, as against 54% in their patients of all ages. This surprisingly good result is attributed to the fact that in these patients the efficacy of a comprehensive regimen had not been vitiated by previous treatment. Of the 97 patients who had had no previous treatment, 88 (90%) were cured, while of the 32 who had had previous treatment only 16 (50%) were cured. The discrepancy between the authors' figures and those of other speakers at the recent International Conference in Toronto is considered to be due to the "antibiotic virginity" of the authors' patients on admission. The incidence of sclero-emphysematous reactions and bullous

dystrophies among these elderly patients was above average, but it is too early to assess their ultimate effect on the course of the disease. The relapse rate was lower than that for the patients of all ages. Relapses responded in 5 cases out of every 8 to a further course of antibiotic treatment.

Norman F. Smith

742. The Role of Bronchoscopy in Primary Pulmonary Tuberculosis in Children

W. F. RICHARDS. *British Journal of Diseases of the Chest* [Brit. J. Dis. Chest] 56, 49-56, April, 1962, 6 figs., 18 refs.

From general experience in the management of cases of primary tuberculosis at Black Notley Hospital, Braintree, Essex, and from a survey of the relevant literature, the author reviews the part played by bronchoscopy in primary tuberculosis in children. [Statistics or chemical data of any kind relating to his own material are not provided.] The main conclusions are as follows. All cases of bronchial obstruction cannot be dealt with adequately at bronchoscopy, but this procedure may be helpful in a proportion of cases in which granulation can be removed. In other cases bronchoscopy may reveal an urgent need for thoracotomy. The indications for bronchoscopy are: (1) stridor and acute respiratory embarrassment, especially in children under 2 years of age; (2) pent-up pus in the bronchi, especially in recent lesions; (3) obstructive emphysema, when bronchoscopy may prevent subsequent collapse; and (4) segmental or lobar collapse, but in such cases bronchoscopy rarely achieves re-expansion of the collapsed segment, unless the collapse occurred less than 3 weeks previously.

John Lorber

743. Distribution of Serum Lipids in Tuberculous Patients and Its Relation to Clinical Coronary Heart Disease

R. STRAUS, M. WURM, W. E. MYERS, and D. SALKIN. *American Journal of Clinical Pathology* [Amer. J. clin. Path.] 37, 339-349, April, 1962, 3 figs., bibliography.

The authors point out that in 1956 in the U.S.A. there were 14,400,000 men aged between 52 and 70 years and that "in this segment of the population during that year" the mortality from "arteriosclerotic heart disease including coronary disease" was 0.81%. In 3,997 tuberculous patients seen over a 7-year period at the Veterans Administration Hospital, San Fernando, California, the mortality from coronary heart disease was only 0.27% in spite of the high-fat, high-calorie diet and the sedentary life of patients in a sanatorium.

The incidence of arteriosclerosis and the blood levels of lipids and lipoproteins were studied in 67 tuberculous patients aged 51 to 70 and the findings compared with those in two groups composed respectively of healthy subjects and "atherosclerotic patients". The blood cholesterol, phospholipid, and total lipid content in the tuberculous patients was found to be significantly lower than in the control groups. The beta:alpha lipoprotein ratio (the atherogenic index) was almost identical with that in the healthy subjects (1.70:1 and 1.81:1) but differed significantly from the index in the atherosclerotic group (3.22:1). One tuberculous patient with a high ratio (5.63:1) subsequently had a coronary thrombosis.

The authors consider that pulmonary tuberculosis may have some protective effect against coronary-artery disease as a result of the part played by the lungs in lipid metabolism. They point out that the lungs, like the liver, may inactivate

circulating lipoprotein lipase and claim that disease of the lungs may affect lipoprotein distribution, thus decreasing atherogenesis.

A. E. Wright

744. Relationship between Pulmonary Tuberculosis and Arteriosclerotic Heart Disease. (Rapporti fra tubercolosi polmonare e miocardiopatia di origine aterosclerotica)

G. PASTEGA and L. POLO. *Minerva medica* [Minerva med.] 53, 982-989, March 31, 1962, 5 figs., 25 refs.

The association of arteriosclerotic heart disease and pulmonary tuberculosis has received attention in recent years because of the increased number of men over 50 who develop tuberculosis. Of 2,224 patients admitted during the 4 years 1957-60 to the A. De Giovanni Sanatorium, Venice, 594 (26.8%) were over 50 years old; 83.4% of them were men. The percentages of patients over 50 in the individual years were: 1957, 22.5%; 1958, 22.3%; 1959, 29.1%; 1960, 33.5%. Of the 594 patients, 66 (10.9%) had arteriosclerotic heart disease; of these, 44 (66.7%) were men and 22 (33.3%) were women. This incidence is the same as that noted by other observers in non-tuberculous subjects in the same age group. The association with tuberculosis aggravated the cardiovascular condition, the adverse effect being greatest in the patients who had had acute episodes of coronary insufficiency and least in those with chronic myocardial sclerosis, the hypertensive cardiopathy group occupying an intermediate position in this respect. The effect of the cardiovascular condition on the tuberculosis was only indirect, and consisted in accentuation of the negative influence of age on resistance to the disease and on response to treatment. The authors stress the importance of accurate diagnosis of the different types of arteriosclerotic heart disease that may occur in association with tuberculosis and make a plea for special therapeutic measures, especially dietetic, in these cases.

A. J. Karlish

745. Acute Tuberculous Perforation of the Small Intestine, with Reports of Four Cases

M. AHMAD. *Journal of the Indian Medical Association* [J. Indian med. Ass.] 38, 317-321, April 1, 1962, 12 refs.

Tuberculosis of the small intestine is common in India. The author, at the Islamia Hospital, Calcutta, saw 12 cases of this condition between April, 1955, and September, 1959, and during the same period he treated 4 cases of acute tuberculous perforation of the intestine. The differential diagnosis is from perforated peptic ulcer and perforated acute appendix. The final diagnosis is made only on the operation table and on the basis of biopsy findings.

Tubercles may or may not be seen on the serous surface of the intestine. The site of perforation is usually in the antimesenteric border of the intestine. Once the perforation has been located it is closed by sutures and single or multiple by-pass operations are performed. Excision should not be a routine procedure. A solution of crystalline penicillin and streptomycin is instilled intraperitoneally, and the cavity is closed without a drain, unless there is gross sepsis, to avoid fistula formation. Full doses of streptomycin are given.

The immediate prognosis appears to be fair, and the long-term prognosis depends on how vigorously the patient follows the antituberculous regimen. Of the 4 patients with perforation 2 had tuberculoma of the ileum, and 2 multiple strictures of the small intestine with tuberculous ulcers which had perforated.

Norman F. Smith

Tropical Medicine

746. Effectiveness of Hydrocortisone and Hydrocortisone-Antivenene Combination Against *Echis carinatus* Snake Venom. [In English]

R. B. ARORA, K. L. WIG, and P. SOMANI. *Archives internationales de pharmacodynamie et de therapie* [Arch. Int. Pharmacodyn.] 137, 299-306, June 1, 1962. 1 fig., 8 refs.

LD₅₀ and LD₉₅ of the *Echis carinatus* venom have been determined for albino rats. Hydrocortisone acetate, given within an hour, was ineffective in 5 mg. per kg. body weight doses against LD₅₀ or LD₉₅ of the venom. In 10 mg. per kg. dose, it protected 57% of the rats against LD₉₅, and 93% of the rats against LD₅₀ of the venom; 20 mg. per kg. dose was found too toxic to be useful. Corticosteroids may prove to be beneficial in snake bite cases when the specific antivenene is not available.

When given with the specific antivenene, hydrocortisone acetate showed a significant potentiating effect in saving the rats against the venom. As the combined therapy is more effective than either of the two drugs given alone, it is recommended in all cases of snake bite by which considerably more lives may be saved than is possible at present.—[Authors' summary.]

747. Fat Metabolism in Malnourished Tropical Children: Some Preliminary Observations

I. MACDONALD. *American Journal of Clinical Nutrition* [Amer. J. clin. Nutr.] 10, 111-113, Feb., 1962. 1 fig., 4 refs.

The author, at Guy's Hospital Medical School, London, has studied the composition of hepatic fat and depot fat in malnutrition and other forms of disease in African children to establish how the lipid metabolism of malnourished children differs from the normal. There are two extreme forms of tropical malnutrition—kwashiorkor and marasmus—which can be differentiated on clinical and aetiological grounds. The former is characterized by gross fatty infiltration of the liver, but there is still a reasonable amount of depot fat; in the latter the depot fat has disappeared.

The author examined liver and depot fat post mortem in 3 groups: 7 cases of kwashiorkor, 5 cases of marasmus, and 24 "control" cases in which the cause of death was not predominantly malnutrition. In the first investigation it was shown that where fat accumulated in the liver there was an increase in the phospholipid fraction in the cases of marasmus and controls, but not in the cases of kwashiorkor. The non-saponifiable fraction was not increased in any group. The degree of unsaturation of the non-saponifiable fraction, however, was higher in those with marasmus than in the controls or the cases of kwashiorkor.

In a further investigation to identify the proportions of the different fatty acids the liver-fat and depot-fat lipids were analysed by gas chromatography. It was found that there was an increase in C₁₈:Δ fatty acid fraction in the liver in kwashiorkor. In the depot fat the C₁₄ and C₁₆ fatty acids were reduced in patients with kwashiorkor compared with the controls, but the C₁₈:Δ were increased. The relative proportions of the different fatty acids in depot fat from

cases of kwashiorkor were very similar to those found in depot fat in European adults. The author points out that liver and depot fats had the same fatty acid composition in kwashiorkor, whereas in the control group the C₁₄ fraction was higher and the C₁₈:Δ and C₁₈:0 fractions were lower in depot fat than in liver fat. This would suggest that the liver in kwashiorkor had become a fat depot.

William Hughes

748. The Artificial Kidney in Malaria and Blackwater Fever

R. C. JACKSON and A. W. WOODRUFF. *British Medical Journal* [Brit. med. J.] 1, 1367-1372, May 19, 1962. 6 figs., 6 refs.

Anuria, as a result of tubular necrosis, is one of the chief causes of death in malaria due to *Plasmodium falciparum* and in blackwater fever. The renal damage is reversible, as has been shown by examination of kidney biopsy specimens, provided the patient can be kept alive long enough for regeneration to take place. The authors describe in detail 4 patients with renal failure following malaria or blackwater fever, 3 of whom were treated by means of an artificial kidney (Kolff twin-coil); one of the 3 patients died, probably from cerebral damage caused by the malarial infection. The fourth patient died on the fifteenth day after renal failure. The biochemical data for each case are detailed.

The authors consider that the following important points are raised by the histories of these 4 patients. Malaria prophylaxis is essential in respect of a visit, even one of as short a duration as 24 hours, to an area in which malaria is endemic. When malaria is considered in the differential diagnosis, blood films should be examined immediately for the presence of parasites. Renal failure should be diagnosed in the oliguric stage, and appropriate treatment instituted at once. The persistent passage of less than 760 ml. of urine a day with a specific gravity of 1.016 or lower denotes a failing kidney. Efficient methods of plasma dialysis are available in certain centres, and patients with renal failure should therefore be sent as quickly as possible to a hospital where such treatment can be given. The old concept that patients in acute renal failure should be nursed where they become ill needs to be revised.

W. H. Horner Andrews

749. The Vibrios of the Recent Cholera-like Outbreak in Hong Kong

S. MUKERJEE and U. K. GUHA ROY. *British Medical Journal* [Brit. med. J.] 1, 685-687, March 10, 1962. 18 refs.

Only very few outbreaks of apparent cholera epidemics, excepting those in the Indonesian archipelago, have been shown to be due to the El Tor vibrio. During the epidemic of para-cholera in Hong Kong in 1961, 130 strains of vibrio were isolated and were shown by haemolytic and phage-sensitivity tests to belong to the El Tor group; of these 130 strains, 129 were of the Ogawa serotype and one of the Inaba serotype, and all gave a positive cholera-red reaction and a negative methyl-red reaction. The result of the Voges-Proskauer test was positive with 126 of the strains and negative with 3. All excepting 3 strains were strongly

haemolytic, and even these 3 showed definite though weak haemolytic properties.

The authors discuss these findings in relationship to immunization and point out that the usual cholera vaccine against *Vibrio cholerae* may be ineffective against disease due to El Tor vibrios. It is clearly important therefore early in an outbreak to identify exactly by means of the phage-sensitivity test the strain of vibrio causing the disease.

W. H. Horner Andrews

750. Significance of Haemoglobins S and C in Ghana

G. R. THOMPSON. *British Medical Journal* [Brit. med. J.] 1, 682-685, March 10, 1962. 32 refs.

The literature on the incidence of haemoglobins S and C in the population of Ghana, about 30% of whom are carriers of one or other of these haemoglobins, is reviewed in this paper from the Military Hospital, Accra. An investigation is then reported of the relationship between haemoglobins S and C and malaria due to *Plasmodium falciparum*. The investigation was carried out in two parts. In the first, which lasted 9 months, thick blood films obtained from all policemen reporting sick with fever in Accra were examined for the presence of malarial parasites; venous blood was also taken for haemoglobin electrophoresis. Since the police are recruited from all over Ghana, the sample was regarded as a cross-section of the whole country. In the second part, which lasted 6 weeks during the wet season, blood was taken for similar examinations from the apparently healthy children, aged 1 to 6 years, of police personnel, the selection being at random. Where indicated, blood was tested for sickling with sodium metabisulphite.

The blood films were positive for malaria in 73 out of 278 adult policemen. They were positive in 48 (25%) of 189 with haemoglobin Type AA, in 19 (36%) of 52 with haemoglobin Type AS, and in 3 (10%) of 30 with Type AC. It is considered that the high incidence of malaria with Type AS haemoglobin may be accounted for by the fact that symptoms developed more readily in this group. In the 840 children examined the carrier rate for all three types of haemoglobins was the same—namely, 28%—but the parasite density was found to be markedly greater in those with haemoglobin AA than in those with the other types of haemoglobin.

It is concluded that haemoglobin C is favourable in the heterozygous state in the presence of *P. falciparum* malaria, and far less disadvantageous in the homozygous state than haemoglobin S.

W. H. Horner Andrews

751. Comparison of Lucanthone Hydrochloride and TWSb in the Treatment of *Schistosoma haematobium* Infection in Tanganyika

P. JORDAN and K. RANDALL. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [Trans. roy. Soc. trop. Med. Hyg.] 56, 136-142, March, 1962. 19 refs.

A trial was carried out at the East African Institute for Medical Research, Mwanza, Tanganyika, to compare the effectiveness of lucanthone hydrochloride and of sodium antimony dimercaptosuccinate (TWSb) in the treatment of school-children infected with *Schistosoma haematobium*. Some of the children also had *S. mansoni* ova in their stools.

Lucanthone was given by mouth in a dosage of 10 mg. per kg. body weight twice daily for 3 days to a total of

60 mg. per kg. TWSb was given intramuscularly on each of 3 successive days in a dosage of 0.5 g. to children weighing over 45 kg., and of 0.4 g. to children weighing between 35 and 45 kg. Some patients were also given three 250-mg. capsules of dimercaptosuccinic acid (DMS), at the time of the injections of TWSb, in order to ascertain if DMS reduced the side-effects of the latter. Miracidia were found in 2 out of 15 patients 4 months after treatment with lucanthone hydrochloride, while 9 out of 14 with *S. mansoni* infection were still passing ova 4 months after treatment with that drug. Of 9 cases treated with TWSb alone, only one had hatchable and unhatchable ova in the urine, whereas of 17 treated with TWSb and DMS, 6 had hatchable ova and one had unhatchable ova. All 8 patients with *S. mansoni* infection were still passing ova after treatment with TWSb (with and without DMS). The incidence of side-effects with both lucanthone hydrochloride and TWSb was high. The simultaneous administration of DMS reduced the side-effects of TWSb but also reduced its efficacy.

While the results of the trial suggest that *S. haematobium* in East Africa is susceptible to both lucanthone hydrochloride and TWSb, the side-effects of both drugs prevent their use on a large scale in control schemes.

P. T. Main

752. Ambulant Treatment of Urinary Schistosomiasis with Astiban (TWSb/6)

G. BARUFFA. *Transactions of the Royal Society of Tropical Medicine and Hygiene* [Trans. roy. Soc. trop. Med. Hyg.] 56, 143-148, March, 1962. 11 refs.

This report from the Società Agricola Italo Somala, Villa-bruzzi, Somalia, describes how 274 patients with *Schistosoma haematobium* infection were treated with different salts of antimony dimercaptosuccinic acid. Magnesium (or potassium) antimony dimercaptosuccinate (TWSb/1) was given to 72 of the cases, and sodium antimony dimercaptosuccinate (TWSb/6 or "astiban") to 149. A few patients were excluded at the start of the trial because their courses of treatment had been experimental, but it was possible to evaluate the tolerance of the drugs in 221 patients and the therapeutic response in 171. Intramuscular administration was found to be more effective than intravenous and the optimum total dose was 40 mg. per kg. body weight given over a maximum period of 10 days. The 4-month presumptive cure rate varied from 70 to 100% according to the different courses followed. The injections were well tolerated locally (those of TWSb/6 better than those of TWSb/1) and side-effects were said to be infrequent (although 66% of the patients vomited when the course was given over a period as short as 3 to 4 days, 28 had joint pains during treatment, and 12 had transient skin rashes). Lengthening the intervals between injections helped to reduce the incidence of side-effects; the therapeutic activity did not seem to decrease in proportion to the decrease in intolerance, provided the total course did not last more than 8 to 10 days.

The author considers that TWSb/6, although not the ideal drug, does represent a significant advance in the ambulatory treatment of urinary schistosomiasis.

P. T. Main

753. Furaltadone in the Treatment of Rhodesian Sleeping Sickness

K. ADRIAENSSENS. *Tropical and Geographical Medicine* [Trop. geogr. Med.] 14, 171-182, June, 1962. 15 refs.

Allergy

754. The Association between Asthma and Tuberculosis

B. GANDEVIA. *Journal of Allergy [J. Allergy]* 33, 112-129, March-April, 1962. 34 refs.

At Gresswell Sanatorium, Melbourne, Australia, among 220 patients with active pulmonary tuberculosis 33 cases of asthma were found—that is, patients with continuous or intermittent wheezing dyspnoea responsive to bronchodilator drugs. In 15 of these the asthma had started long before the tuberculosis, 11 of them having allergic asthma. In 6 cases the tuberculosis had preceded the asthma, and in 8 cases both conditions had started simultaneously. There were also 4 patients with occupational lung fibrosis. In none of these last 18 patients was an allergic aetiological factor found. Cutaneous tuberculin sensitivity was similar in the asthmatic and non-asthmatic patients, and no specific relationship between the two conditions was found in the past histories of the patients.

H. Herxheimer

755. The Effect of Exercise on Ventilatory Function in the Child with Asthma

R. S. JONES, M. H. BUSTON, and M. J. WHARTON. *British Journal of Diseases of the Chest [Brit. J. Dis. Chest]* 56, 78-86, April, 1962. 8 figs., 5 refs.

The study reported in this paper from the University and Alder Hey Children's Hospital, Liverpool, was designed to determine the effect of the duration of exercise on ventilatory function in 21 asthmatic children. The exercise consisted in running, the level of the exercise being adjusted to the tolerance of the individual with the object of producing moderate breathlessness. The forced expiratory volume (F.E.V.) was measured [for technical details the paper should be consulted]. It was found that exercise of short duration, that is, lasting 1 to 2 minutes, produced an increase in the F.E.V. within one minute of the end of the exercise. Prolonged exercise for 8 to 12 minutes produced a decrease in the F.E.V., which reached a minimum value between 1 and 5 minutes and then rapidly increased toward the resting level. The level of the exercise determined the degree of these ventilatory effects. Both the increase and the decrease were minimized by preliminary inhalation of an aerosol of isoprenaline sulphate, suggesting that the phenomena are due to changes in the airways resistance caused by bronchodilatation or bronchoconstriction in bronchi which are already to some extent constricted.

John Lorber

756. Betamethasone in the Treatment of Bronchial Asthma

J. H. TOOGOOD. *Canadian Medical Association Journal [Canad. med. Ass. J.]* 86, 273-278, Feb. 10, 1962. 1 fig., 6 refs.

Preliminary tests of the therapeutic activity of betamethasone in asthma were carried out on 15 patients at Victoria Hospital, London, Ontario, who had failed to respond to conservative measures. In all cases good control was obtained within 6 days; in 8 cases long-term treatment was continued with a maintenance dose of 0.5 to 1 mg. daily. Side-effects in 8 cases were acne, gain in weight, increased appetite, depression, flushing, hirsuties, or a

combination of these, and necessitated discontinuance of treatment in one case. Flushing usually disappeared after 48 hours' treatment with the drug.

After this trial the dosage equivalents of betamethasone and prednisone were compared in 22 patients. Betamethasone appeared to be 10 to 15 times more potent weight for weight than prednisone, the minimum effective daily dose being 0.6 to 1 mg.

R. S. Bruce Pearson

757. Fluprednisolone, a New Corticosteroid, in Treating Allergies

S. M. FEINBERG, A. R. FEINBERG, and E. W. FISHERMAN. *Journal of New Drugs [J. New Drugs]* 1, 268-270, Nov.-Dec., 1961 [received April, 1962]. 1 fig., 2 refs.

Fluprednisolone, a compound with a fluorine atom at the 6 α -position in prednisolone, was given to 159 patients attending the Allergy Unit, Northwestern University Medical School, Chicago. The majority of the patients (about 70%) were asthmatic and these responded to smaller doses than did those with allergic rhinitis. Fluprednisolone was then compared with 4 other corticosteroids for its ability to maintain 85 out of the 159 allergic patients. Weight for weight it was more potent than prednisolone, methylprednisolone, and triamcinolone, but less potent than dexamethasone. In general, the side-effects were similar to those produced by other corticosteroids. Water retention with the usual maintenance dose was encountered only rarely. Fluprednisolone appeared to reduce the incidence of such side-effects as mooning, ecchymoses, and muscle cramps.

G. B. West

758. Cross-allergenicity of Penicillin G and Related Substances

G. T. STEWART. *Lancet [Lancet]* 1, 509-510, March 10, 1962. 11 refs.

At Queen Mary's Hospital for Children, Carshalton, Surrey, 4 adult volunteers and one child who were all known to be hypersensitive to benzylpenicillin were given test intradermal injections of 5 other penicillins. All the subjects reacted to *p*-aminobenzylpenicillin, dimethoxybenzylpenicillin (methicillin), α -aminophenylacetamido penicillanic acid (ampicillin), and to a specially purified sample of 6-amino penicillanic acid (6-APA); 3 who were repeatedly tested with cephalosporin C failed to react to it.

Reports on antigenic cross-reactions between cephalosporin N and benzylpenicillin are contradictory (Berryman and Fisherman, *J. Allergy*, 1959, 30, 329; L  y et al., *Science*, 1958, 127, 1118). Cephalosporin N has a straight side-chain instead of the more usual cyclic benzyl side-chain, whereas cephalosporin C, which has the cyclic side-chain, possesses a 6-membered dihydrothiazine ring instead of the 5-membered thiazolidine ring (6-APA) shared by the other compounds. It appears therefore that cross-allergenicity with benzylpenicillin depends upon the 6-APA nucleus itself and that the presence of the usual cyclic side-chain does not abolish the allergenicity, though it is not certain if a straight side-chain may modify it.

Janice Taverne

Nutrition and Metabolism

759. Studies on Growth in Refractory Rickets

R. STEENDUK. *Journal of Pediatrics* [*J. Pediat.*] **60**, 340-345, March, 1962. 4 figs., 15 refs.

It is known that rickets is usually more severe in rapidly growing than in slowly growing children, but little is known about the effect of rickets on growth. In this study, from the University of Amsterdam, of 4 patients, 2 boys and 2 girls, with primary refractory rickets, the height, bone age, and clinical state during puberty were observed.

It was found that the pubertal spurt in growth took place in all the patients but that, in all except one in whom the disease was subclinical, the rate of growth was subnormal. Radiologically, there was no increase in rachitic activity in 3 of the 4 patients. Increase of deformities of the legs occurred in 2, and in one the growth spurt was accompanied by the onset of slight deformities of the legs. The short stature of all the patients was attributable to shortness of their legs, since the spines were of normal length and shape. It is suggested that deformity is the most important growth-limiting factor. No conclusive evidence that rickets directly delays growth was obtained.

B. M. Ansell

760. Fasting Ketosis in Obese Men and Women

W. L. BLOOM. *Journal of Laboratory and Clinical Medicine* [*J. Lab. clin. Med.*] **59**, 605-612, April, 1962. 1 fig., 9 refs.

Previous studies have suggested that, during fasting, ketonuria is less in obese than in lean subjects and in males than in females. At Piedmont Hospital, Atlanta, Georgia, the changes in the blood level and urinary excretion of ketones were studied in 6 obese males and 7 obese females while they fasted and their activity was limited and comparable. No significant difference was observed between males and females in the blood and urine levels of ketones. Comparison of the findings in these obese patients with those in lean patients previously reported suggested that in comparable periods of fasting obese men and women excreted fewer ketone bodies than lean patients. Obesity appeared to abolish female susceptibility to ketosis. It is pointed out that since in previous studies the part played by energy expenditure was not controlled, the observed differences could be due to activity as a variable rather than sex or obesity. Until the results of more controlled experiments are available the evidence so far suggests that obesity increases the resistance of both sexes to ketosis as well as abolishing the sex difference in susceptibility.

A. G. Mullins

761. Treatment of Wilson's Disease (Hepatolenticular Degeneration) with DL-Penicillamine

N. P. GOLDSTEIN, R. V. RANDALL, J. B. GROSS, J. W. ROSEVEAR, and W. F. MCGUCKIN. *Neurology* [*Neurology (Minneapolis)*] **12**, 231-244, April, 1962. 7 figs., 14 refs.

The authors describe 7 cases of hepatolenticular degeneration (Wilson's disease) seen at the Mayo Clinic since 1955, 5 of which have been previously reported (Litin *et al.*, *Neurology (Minneapolis)*, 1960, 10, 123). In 6 cases the dura-

tion of treatment with DL-penicillamine given orally was 17 to 33 months and the usual daily dose ranged from 200 to 1,500 mg. In the remaining case this treatment could be given for only 4 weeks owing to the development of toxic reactions, and this patient died from progressive hepatic failure. In 5 of these cases treatment with dimercaprol (BAL) was tried at some time during the course of the disease, and the authors conclude that the urinary excretion of copper and the clinical response were both better with penicillamine than with BAL.

[From the authors' review of previous reported results it is apparent that in some of the cases of this disease the response to penicillamine was not so satisfactory as that obtained with BAL, while in others the reverse was the case. In view of this variability of response to treatment, it would seem that penicillamine should be the initial drug of choice, since from the patient's point of view the oral administration of penicillamine is far preferable to treatment with BAL, which involves frequent and painful injections.]

A. G. Freeman

762. The Effect of Diets of Different Composition on Weight Loss, Water and Sodium Balance in Obese Patients

G. F. M. RUSSELL. *Clinical Science* [*Clin. Sci.*] **22**, 269-277, April, 1962. 3 figs., 15 refs.

Why different kinds of low-calorie diet vary in their effectiveness when given to obese patients for short periods of time has been the subject of conflicting evidence and argument.

In an investigation carried out at the Maudsley Hospital, London, 3 obese patients were given for 7 to 11 days three different diets in which most of the calories were derived from carbohydrate, protein, and fat respectively. Changes in body water were studied by the most sensitive method available—that is, performance of metabolic water balances—and the contribution of fluctuations in water balance and the daily changes in body weight were determined. The intake of sodium and water was also kept constant.

During feeding with a high-carbohydrate diet the amount of weight lost was reduced and the water and sodium balances became positive. On a diet relatively rich in protein or fat there was a sharp loss of weight accompanied by negative water and sodium balances. The balance of water and sodium, as well as the urinary volume, were highly correlated with daily fluctuations in body weight. It is concluded that the fluctuations in weight produced by varying the composition of the diet are caused by alterations in the water content of the body, mediated entirely by variations in the urinary excretion of water. The shifts in the balance of water are accompanied by changes in the balance of sodium of such an order as to maintain isotonicity of the body fluids.

A. G. Mullins

763. Clinical Aspects of Inborn Metabolic Defects

P. R. EVANS. *Proceedings of the Nutrition Society* [*Proc. Nutr. Soc.*] **21**, 12-20, 1962. 1 fig., 25 refs.

Gastroenterology

764. Differences in Absorption of the Various Fatty Acids Studied in Children with Steatorrhea

J. FERNANDES, J. H. VAN DE KAMER, and H. A. WEIJERS. *Journal of Clinical Investigation [J. clin. Invest.]* 41, 488-494, March [received May], 1962. 8 figs., 22 refs.

This paper from the Central Institute for Nutrition and Food Research TNO, Utrecht, Netherlands, describes the variation in absorption of a number of fatty acids in 8 children with coeliac disease, 7 with pancreatic cystic fibrosis, and one with steatorrhea following ileal resection. The fat to be tested was added to a basic low-fat diet. On the basic diet, excretion of fat was less than 2 g. per day. The amount of fat given varied from 40 to 80 g. per day, depending on age. Each balance period comprised at least 2 days of fat feeding followed by a 2- to 3-day collection period while the patient was on the same test diet. Analyses of dietary and faecal fats were expressed as coefficients of excretion for the test fatty acids—that is, the ratio of fatty acid in faeces to that in the test diet, expressed as a percentage.

In coeliac disease it was found that the absorption of fatty acids is dependent upon chain lengths, absorption diminishing with increase in molecular size. The degree of saturation is also important, those fatty acids with one or more double bonds being more readily absorbed than the more saturated ones. Finally, it was observed that the extent of absorption of any fatty acid depends upon the composition of the dietary fat, the fatty acid being more readily absorbed when fed with other fatty acids which are relatively poorly absorbed.

The differences in absorption of the various fatty acids in patients with pancreatic cystic fibrosis were less marked than in those with coeliac disease. It is suggested that this is due to an incomplete intestinal hydrolysis in the former condition.

The authors conclude that patients with steatorrhea may benefit from the ingestion of fats composed of unsaturated fatty acids.

Hewett A. Ellis

765. Carcinoma of the Pancreas

S. F. PHILLIPS and W. E. KING. *Medical Journal of Australia [Med. J. Aust.]* 1, 541-545, April 14, 1962. 22 refs.

The authors, from the Royal Melbourne Hospital, describe their experiences of the symptomatology of 40 patients with carcinoma of the pancreas, diagnosis being made at laparotomy, at necropsy, or by biopsy. Obstructive jaundice was the presenting symptom in 17 patients, occurred later in another 5, and was never present in 18; 15 patients presented with abdominal pain, and 14 of the 17 initially jaundiced patients also developed pain. Other presenting symptoms included anorexia and vomiting (3 patients), ascites (2), chest pain due to pleural metastases (1), multiple venous thromboses (1), and mental disturbances (1); 37 patients had lost between 7 and 28 lb. (3.175 and 12.7 kg.) in body weight, and 8 had glycosuria. (Four of these 8 patients were already known to be diabetics.) Four patients gave a family history of pancreatic carcinoma. In one family the father, daughter, and son died from the disease.

Of the 40 patients, 29 were considered to show clinical evidence of metastases at the time of presentation.

Hewett A. Ellis

STOMACH AND DUODENUM

766. The Site of Upper Gastrointestinal Bleeding: Detection by Radioactive-tagged Red Blood Cells

I. M. ARIEL. *Journal of the American Medical Association [J. Amer. med. Ass.]* 180, 212-214, April 21, 1962. 10 refs.

A simple and safe technique is described for determining whether gastro-intestinal bleeding occurs from the oesophagus or from the stomach and duodenum. An intravenous injection of 10 ml. of the patient's own blood labelled with 100 μ c. of radioactive chromium is made and the radioactivity of gastric and oesophageal aspirate determined. A Necheles tube is used for sealing the junction between stomach and oesophagus and separating the aspirates.

Of 15 patients examined in this way, oesophageal bleeding was detected in 5 and gastric or duodenal bleeding in 6; one of the latter patients had both a duodenal ulcer and severe cirrhosis. Subsequent radiography or surgery confirmed the site of the bleeding. The test was unsatisfactory in 4 patients because bleeding had ceased.

A. Wynn Williams

767. Giant Gastric Ulcer: Report of 27 Cases

S. ZATERKA, A. BETTARELLO, J. DE S. MEIRELES FILHO, M. R. MONTENEGRO, and J. F. PONTES. *American Journal of Digestive Diseases [Amer. J. dig. Dis.]* 7, 236-249, March, 1962. 10 figs., 20 refs.

It has been contended that large gastric ulcers (defined as ulcers with a diameter of over 3 cm.) are malignant. The authors report in this paper from the University of São Paulo, Brazil, 27 cases of giant ulcer (diameter 3 cm. or more) seen in a larger series of 300 cases of gastric ulcer over a 13-year period. In all cases the stomach was examined radiologically, while in 16 gastroscopy was carried out and in 9 the gastric cytology was studied. From the findings a malignant condition was diagnosed initially in 9 cases; operation was performed in 6 of these, but the lesions were found to be malignant in 2 only. The remaining patients in the series, in whom there was no evidence initially of malignant disease, were given conventional medical treatment—frequent light feeds together with alkalies, anticholinergic drugs, sedatives, and rest in bed for 4 weeks. At the end of this period the special investigations were repeated. If after 4 weeks the ulcer had not decreased in size or after 8 weeks it had not disappeared it was considered to be malignant and operation was advised. Of the 18 patients given this "therapeutic test" 5 showed healing of the ulcer at 8 weeks but symptoms returned in 3, necessitating operation in 2, one of whom had a lymphosarcoma and one a benign ulcer. Of the 13 patients in whom ulcers persisted after treatment 7 were operated on; of these, 5 had benign gastric ulcers, one a degenerated ulcer, and one a gastric carcinoma. In 4 of the 6 patients who did not undergo operation the lesion disappeared within 13 months of treatment. The 2

remaining patients were still alive, one undergoing treatment. The only serious complication in the patients with benign gastric ulcers was haemorrhage, although chronic pulmonary emphysema was noted in 6. It is emphasized that size alone should not be relied upon as a criterion of the benign or malignant nature of an ulcerated gastric lesion. In the authors' series 4 patients with benign ulcers were subjected to extensive surgery and 3 died as a result of the operation. Giant ulcers may heal as well as small ones, although recurrences are more common with the former. The concept of the "pseudomalignant" gastric ulcer is discussed, such an ulcer possessing all the characteristics of a malignant ulcer except the histological appearances.

J. Warwick Buckler

768. Partial Gastrectomy for Duodenal Ulcer

C. G. CLARK and N. J. LOGIE. *Journal of the Royal College of Surgeons of Edinburgh [J. roy. Coll. Surg. Edinb.]* 7, 209-216, April, 1962. 2 figs., 7 refs.

The late results of partial gastrectomy of the Polya type for chronic duodenal ulcer are described. The series included 449 patients operated on at one of three surgical units in Aberdeen during the years 1945-55 and followed up, usually by interview, in 1960. The operative mortality was 7% (32 patients), the commonest cause of death being a leak from the duodenal stump. A further 5.3% (24 patients) died in the intervening years. Of the remaining 393 patients 331 (84.3%) were traced.

Late results were classified as "excellent" in 61.3%, "good" in 26.3%, "poor" in 7.3%, and "failed" (proven recurrent ulcer) in 5.1%. The higher the level of the gastric resection the greater were the postcibal disturbances, while the lower the level the greater the risk of stomal ulceration. It was also found that weight loss correlated with eating capacity. Hypochromic anaemia was common and 13 (4%) of the patients had had active tuberculosis since the operation.

B. F. Swynnerton

769. Variations of Duodenal Diverticula; Source of Occult Bleeding

M. M. KLEIN, E. GRIBOVSKY, and R. L. BRADLEY. *American Journal of Gastroenterology [Amer. J. Gastroent.]* 37, 370-381, April, 1962. 7 figs., 14 refs.

Duodenal diverticula were demonstrated radiologically in 130 (3.08%) of 4,260 patients, with gastro-intestinal lesions seen over a 10-year period. Only males were affected, most commonly in the 5th and 6th decades. In 23.2% of patients the lesions were multiple; they occurred in any part of the duodenum, but most commonly in the second part. Two types were recognized: false, due to associated ulceration, and true, which were mucosal herniations through the muscle coats. The aetiology of the latter is uncertain, but in 21 cases (16.1%) diverticula were present in other parts of the gastro-intestinal tract. Clinical manifestations included melaena and anaemia, abdominal discomfort and tenderness, and nausea.

A. Wynn Williams

770. Immediate Results of Subtotal Gastric Resection for Benign Peptic Ulcer

R. R. PAINE. *Surgery [Surgery]* 51, 561-568, May, 1962.

During the ten-year period from Jan. 1, 1950, to Jan. 1, 1960, at the Buffalo General Hospital, New York, 684 patients with benign peptic ulcers of the stomach or duo-

denum were subjected to subtotal gastric resection. The over-all hospital mortality rate was 5.7%. For patients with duodenal ulcers the mortality rate was 6% and for patients with gastric ulcers the mortality rate was 4.9%. Approximately one-third of the patients were operated upon because of bleeding from the upper gastrointestinal tract. The mortality rate for patients who needed transfusion of more than 1,000 c.c. of blood prior to operation was 16%. Patients in this category accounted for one-half of the total deaths. Major postoperative complications occurred in approximately one-third of the patients. One-half of the complications were some type of infection involving either the abdominal incision or the peritoneal cavity. Twenty-four of the 39 deaths in this series of patients were the direct consequence of some technical failure.

Means by which the mortality and morbidity rates of subtotal gastric resection could possibly be decreased are discussed.—[Author's summary.]

771. Results of Surgical Treatment of Peptic Ulcer

E. S. STAFFORD and G. G. FINNEY. *Annals of Surgery [Ann. Surg.]* 155, 687-695, May, 1962. 8 refs.

During a period of 14 years the authors operated upon 252 consecutive patients who had prepyloric gastric or duodenal ulcers. Of these, 196 patients had pain unrelieved by medical therapy as their chief indication for operation and in this group there was but one postoperative death. A group of 33 patients were operated upon for massive bleeding and 2 of these died after operation. There were no deaths among 23 patients operated upon primarily for obstruction. It has been possible to follow until now the results of treatment in 227 of these patients. In only 3.0% is the result judged poor and in some this judgment is based on subjective criteria. Careful selection, for each individual, of the proper operative procedure and proper postoperative indoctrination have been considered to be the most important factors in obtaining these good results. Gastric resection (60 to 70%) was the most frequently used operation (217 patients).—[Authors' summary.]

772. Selective Surgery for Peptic Ulcer: a Review

I. M. ORR. *Gut [Gut]* 3, 97-105, June, 1962. 1 fig., 26 refs.

LIVER AND GALL-BLADDER

773. Studies with I¹³¹-labeled Rose Bengal. I. Derivation of a Technic for Use in the Differential Diagnosis of Jaundice

M. KAWAGUCHI, A. R. SOBLE, and J. E. BERK. *American Journal of Digestive Diseases [Amer. J. dig. Dis.]* 7, 289-299, April, 1962. 5 figs., 21 refs.

The authors have used rose bengal (tetraiodo-tetrachloro-fluorescein) labelled with radioactive iodine (¹³¹IRB) as a diagnostic aid in the differential diagnosis of jaundice. In this report from the Sinai Hospital (Wayne State University), Detroit, they describe their technique as used in control subjects and patients with hepatobiliary disease in whom surface counting over the liver was performed after the intravenous injection of 10 to 15 μ c. of ¹³¹IRB. The counts, by means of careful timing, were made a function of liver-cell uptake and not of hepatic blood flow. In the

normal subjects hepatic uptake was estimated to range from 12 to 26% (mean $19.0 \pm 3.8\%$) of the injected dose. The excretion of ^{131}IRB into the intestine from the gall-bladder was measured following the intravenous injection of 3 mg. of cholecystokinin. By counting over the area of maximum activity (the gall-bladder) 1 hour after the injection of ^{131}IRB and noting the decline in activity at this point as well as the increased activity as detected by a mid-abdominal counter after the administration of cholecystokinin, entry of ^{131}IRB into the intestine was assessed.

Of 19 normal subjects 12 demonstrated a decline in gall-bladder activity, but in 7 of the patients irregular and bizarre results were obtained, perhaps owing to abnormal intestinal activity induced by the cholecystokinin. Because of these inconstant results the authors reassessed the method, this time using sodium dehydrocholate (10 ml.) and nitroglycerin (0.6 mg.), and by this means obtained more satisfactory results. The excretion of ^{131}IRB into the intestine was again calculated from recorded activity over the mid-abdomen. By comparing liver uptake (L.U.) and intestinal entry (I.E.) and expressing these factors as a ratio it was noted that patients with hepatocellular disease had an I.E.:L.U. ratio of over 17, whereas in those with extrahepatic obstructive jaundice the ratio was below this figure.

A. E. Read

774. Studies with ^{131}I -labeled Rose Bengal. II. Clinical Evaluation of a Modified Technique for Differential Diagnosis of Jaundice

M. KAWAGUCHI, J. E. BERK, and A. R. SOBLE. *American Journal of Digestive Diseases* [Amer. J. dig. Dis.] 7, 300-308, April, 1962. 3 figs., 25 refs.

Using the technique described above [see Abstract 773] as a diagnostic aid in the differential diagnosis of jaundice the authors have determined the liver uptake (L.U.) and intestinal entry (I.E.) of ^{131}IRB as derived from the radioactivity over the liver and intestine in 104 subjects—43 controls and 61 patients with various forms of hepatobiliary disease.

The value for L.U. in normal subjects ranged from 19 to 37% (of the total dose administered). Patients with hepatobiliary disease and malignant biliary obstruction showed the lowest values for L.U.; in those with malignant biliary obstruction L.U. was usually lower than in those with non-malignant obstruction, the mean difference between these two groups being statistically significant. Values for I.E. after administration of "decholin" (sodium dehydrocholate) were uniformly lower in patients with intrahepatic cholestasis and extrahepatic obstruction, in all cases being below the lowest value in normal subjects. However, there was an overlap in I.E. values between normal subjects and patients with hepatobiliary disease with and without jaundice. In patients with malignant extrahepatic obstruction a difference in I.E. was again noticeable as compared with those with non-malignant obstruction, I.E. being significantly lower in the former group.

A comparison of the I.E.:L.U. ratio showed that this differed markedly between patients with hepatocellular jaundice and those with non-malignant extrahepatic obstruction. Thus in 22 of the former it was over 17, whereas in 12 patients with non-malignant extrahepatic obstructive jaundice and 6 out of 9 with malignant obstruction it was less than 17. Of the 3 patients with malignant obstruction

but a high I.E.:L.U. ratio it was noted that there was evidence of severe secondary hepatic damage. The authors conclude that this test is of value in differentiating the cause of jaundice if used in the way they describe. The occurrence of low values for both L.U. and I.E. should draw attention to the possibility of malignant extrahepatic obstruction, even though the I.E.:L.U. ratio may exceed the critical range for obstruction. Intrahepatic cholestasis tends not to be clearly differentiated from hepatocellular jaundice, and it is noted that in cases of gross hepatomegaly the widespread scatter of radioactivity may lead to erroneous results. Ascites, on the other hand, does not interfere with the test, provided all three measurements are made conjointly.

A. E. Read

775. Causes and Diagnosis of Jaundice in the Elderly

A. HUETE-ARMJO and A. N. EXTON-SMITH. *British Medical Journal* [Brit. med. J.] 1, 1113-1114, April 21, 1962. 1 fig., 9 refs.

This paper on certain aspects of the semiology of jaundice in old age analyses a group of 80 patients aged between 65 and 89 years who presented with jaundice at the Whittington Hospital, London. The authors draw some obvious conclusions—namely, that obstructive jaundice is the commonest form encountered and that it is due to cancer in 44% of cases. They also point out that calculous jaundice is not infrequently painless. They call attention to the fact that many drugs in current use can and do cause jaundice, chlorpromazine being most often responsible in the elderly. [The authors are to be congratulated on a 90% accuracy of clinical diagnosis.]

P. D. Bedford

776. Prophylactic Portacaval Anastomosis in Cirrhotic Patients with Esophageal Varices: a Preliminary Report of a Controlled Study

H. O. CONN and W. W. LINDENMUTH. *New England Journal of Medicine* [New Engl. J. Med.] 266, 743-749, April 12, 1962. 2 figs., 36 refs.

It is now well authenticated that the surgical formation of a portacaval shunt decreases the incidence of recurrent haemorrhage from oesophageal varices in cirrhotic patients. Only the fittest patients are chosen for this operation, and it is still an unsettled question whether the prognosis of the condition is really improved by the formation of such a shunt.

In this paper from Yale University School of Medicine the progress of 15 cirrhotic patients in whom a prophylactic shunt was performed is compared with that of 18 similar patients not subjected to this procedure. The authors also consider the history of 8 patients with a therapeutic shunt made because of bleeding oesophageal varices, and of 8 patients who were for various reasons considered to be unsuitable for prophylactic operation. The two main groups were approximately similar in regard to their clinical condition.

Patients were observed for between 5 months (unless death occurred earlier) and 2½ years, the average being about 14 months. One patient in the control group died from haemorrhage, and 2 in the group with prophylactic shunts died, one from the operation and the other from haemorrhage after the shunt had become obstructed by thrombosis. Although the incidence of haemorrhage was lower in the operated group, the mortality, on the other hand, was

slightly greater than in the control group. There was some reduction in the severity of the varices in both groups, but the difference between the groups was not significant. A further period of study is therefore necessary before it is possible to demonstrate whether the dangers of haemorrhage from oesophageal varices outweigh the risks of portal decompression carried out as a prophylactic measure in reasonably fit patients.

W. H. Horner Andrews

777. Primary Liver Neoplasms: a Review of 20 Cases

R. R. MORGAN, M. FERGUSEN, and W. J. GRACE. *American Journal of Digestive Diseases* [Amer. J. dig. Dis.] 7, 309-317, April, 1962. 2 figs., 13 refs.

The authors have made a retrospective study of tumours of the liver based on reports of necropsies performed at St. Vincent's Hospital, New York City, during the years 1953-9. There were 19 hepatomata and one cholangiocarcinoma, and all but 2 of these neoplasms were associated with cirrhosis of the liver. The clinical picture was usually that of a rapidly progressing cirrhosis with abdominal pain or distension as the main complaint. Gastro-intestinal bleeding occurred in 9 cases, and this appeared to be due to portal hypertension with oesophageal varices. All patients died within one month of admission, usually in hepatic coma. At necropsy ascites was present in 16 cases, and in 6 the fluid was blood-stained. In 13 cases multiple tumours were present.

P. C. Reynell

778. Absorptive Function of the Small Intestine in Liver Cirrhosis

E. BARAONA, H. ORREGO, O. FERNÁNDEZ, E. AMENABAR, E. MALDONADO, F. TAG, and A. SALINAS. *American Journal of Digestive Diseases* [Amer. J. dig. Dis.] 7, 318-330, April, 1962. 7 figs., 42 refs.

Absorption from the small intestine was studied in 74 patients with cirrhosis of the liver (61 of them alcoholics) at the Hospital Clínico of the University of Chile, Santiago. Of 42 patients tested, 30 excreted more than 20 g. of fat in 4 days, and 5 excreted over 60 g. Of 44 patients tested, 21 had a plasma carotene level below the lower limit of normal, and in 25 the urinary excretion of ingested D-xylose was abnormally low. Pancreatic secretion after injection of secretin was measured in 21 patients, and the maximum bicarbonate concentration was found to be low in 13. In only one of the 10 jejunal biopsy specimens available was any atrophy of the villi detected. The authors conclude that intestinal absorption is often impaired in patients with cirrhosis of the liver, though the impairment is rarely severe enough to interfere significantly with nutrition.

P. C. Reynell

779. Malabsorption Syndrome Associated with Anicteric Liver Disease

W. H. J. SUMMERSKILL and C. G. MOERTEL. *Gastroenterology* [Gastroenterology] 42, 380-392, April, 1962. 3 figs., 16 refs.

That malabsorption can be a feature of liver disease associated with retention of bile has long been established. The authors of this paper from the Mayo Clinic draw attention to the occurrence of malabsorption in liver disease when overt signs such as icterus are absent. On examination of 7 patients with fatigue, diarrhoea, and loss of weight but without jaundice when first seen, splenomegaly, a vascular

spider, hepatomegaly, or ascites was found. Liver function tests revealed a normal serum bilirubin level, serum albumin levels ranging from 1.43 g. to 3.1 g. per 100 ml. (normal value more than 3.5 g. per 100 ml.), and "bromsulphalein" retention of 8 to 40% after one hour (normal less than 6% after one hour). This evidence of liver failure was accompanied by evidence of malabsorption by the small intestine. Faecal fat excretion was 26 to 132 g. per hour (normal value less than 18 g. per hour). The serum carotene and serum calcium levels were deficient in all cases, the faecal excretion of nitrogen was abnormal in one case, and in a further 3 cases there was evidence of defective absorption of vitamin B₁₂ labelled with radioactive cobalt. [Testing for pancreatic function was limited and the results of duodenal intubation or secretin studies are not given.]

Biopsy or post-mortem examination revealed changes indicative of cirrhosis or chronic hepatitis, but the small intestine was normal in every case. In 3 patients, however, a deficiency pattern was observed on follow-through of a barium meal. A close relationship was noted between hepatic and absorptive function; improvement in the former was followed by a diminution in malabsorption.

Treatment, which included oral administration of human bile, antibiotics, and prednisolone, pancreatic replacement therapy, and a gluten-free diet, was without benefit. A diet rich in protein and calories but of low fat content with specific replacement of deficiencies was the most effective form of therapy.

J. S. Malpas

780. The Effects of Sodium dextro-Thyroxine on Lipid Metabolism in Primary Biliary Cirrhosis

C. L. MENDENHALL and A. MORTIAUX. *Gastroenterology* [Gastroenterology] 42, 411-413, April, 1962. 3 figs., 15 refs.

At the Royal Free Hospital, London, 4 patients with primary biliary cirrhosis and markedly raised serum cholesterol levels (475 to 875 mg. per 100 ml.) were treated with 2 mg. (and later 10 mg.) of D-thyroxine daily. In all 4 patients there was a reduction in the serum cholesterol level ranging from 27 to 58%, and a rise in the serum free fatty acid content by 51 to 104% during treatment. All the patients complained of a moderate increase in pruritus. The serum bilirubin level showed no consistent alteration. It is suggested that these results indicate that patients with primary biliary cirrhosis are capable of metabolizing greater amounts of cholesterol.

G. S. Crockett

781. Vitamin B₁₂ Content of Liver and Serum in Malignant Neoplasia

R. S. NELSON and V. M. DOCTOR. *Gastroenterology* [Gastroenterology] 42, 414-418, April, 1962. 1 fig., 5 refs.

In the study here reported from Baylor University College of Medicine, Houston, Texas, the vitamin B₁₂ content of the liver was found to be definitely lowered in patients with metastatic malignant disease of the liver, but in these cases low liver levels did not necessarily correspond with high serum levels of the vitamin. An increased serum vitamin B₁₂ level was found in patients with leukaemia or lymphoma; while the liver content was on the average slightly lowered, and again there was no apparent direct correlation between these two findings.

[For the methods of estimation employed reference should be made to the original paper.]

G. S. Crockett

Cardiovascular System

782. Inhalation of Amyl Nitrite: a Useful Test in the Assessment of Heart Murmurs

G. A. BOUSVAGOS and M. H. LESSOF. *Guy's Hospital Reports [Guy's Hosp. Rep.]* 111, 1-12, 1962. 4 figs., 12 refs.

The immediate effect of inhalation of amyl nitrite is to dilate peripheral but not pulmonary vessels, increasing systemic blood flow and reducing systemic pressure to its lowest point in about half a minute, from which it recovers in a further minute or two. Owing to increased venous return there is a temporary rise in right ventricular output after half a minute. Work at Guy's Hospital, London, on patients with acquired and congenital heart disease has confirmed these changes and demonstrated the applicability of amyl nitrite inhalation as a test for identifying heart murmurs. Murmurs due to forward flow of blood are intensified, while those due to regurgitation diminish; thus the systolic murmur of aortic stenosis becomes louder and that of mitral regurgitation softer, and the diastolic murmur of mitral stenosis becomes louder and that of aortic regurgitation softer. Similarly, in the right side of the heart, after a brief delay, the systolic murmur of pulmonary stenosis and the diastolic murmur of tricuspid stenosis increase. In cases of pulmonary stenosis measurements during right heart catheterization show a striking rise in right ventricular pressure and fall in systemic arterial pressure. Where there is a ventricular septal defect, as in Fallot's tetralogy, the pulmonary systolic murmur softens with inhalation of amyl nitrite, for the right-to-left shunt into the systemic circulation increases. With atrial septal defect, amyl nitrite increased the pulmonary systolic murmur and sometimes accentuated or revealed a presystolic murmur due to atrial systole or a diastolic murmur due to rapid inflow through the tricuspid valve. In cases of patent ductus arteriosus the continuous murmur diminished, and sometimes the shunt was reversed, if aortic pressure was made to fall below pulmonary pressure.

J. A. Cosh

783. Clinical Study of Nylin's Heart Function Test

CHU CHEN and MA WAN-SEN. *Chinese Medical Journal [Chin. med. J.]* 81, 251-259, April, 1962. 1 fig., 9 refs.

At the People's Hospital, Peking, exercise tolerance was assessed in 224 healthy adults, who were required to climb and descend a standard staircase at a set pace indicated by built-in light signals. Exercise tolerance and therefore cardiac reserve were estimated by measuring the post-exercise increase in oxygen consumption per unit area of body surface, a Benedict-Roth or Krogh spirometer being used. It was found that the oxygen debt was smaller in females than males. No significant difference was observed between the oxygen debt of fasting subjects and that of non-fasting subjects. This indicates that it is not necessary for patients to fast before exercise tolerance is investigated.

Exercise tolerance was then similarly estimated in 102 patients with various cardiovascular diseases. When the findings were compared with those in the healthy subjects, it was seen that there was a greater oxygen debt in patients with Class-I and Class-II heart disease (American Heart Classification). Patients with Class-III and Class-IV heart

disease were not tested because the symptoms were too severe. The increase in cardiac outline paralleled the increase in oxygen debt. Cardiac catheterization in 16 cases confirmed that an increase in oxygen debt is evidence of decreased cardiac reserve.

It is concluded that Nylin's heart-function test is a simple and effective means of evaluating cardiac function.

D. Goldman

CONGENITAL HEART DISEASE

784. Open Heart Surgery under Selective Hypothermia and Extracorporeal Circulation

CHANG T'EN-HUEI, WANG YUAN-CH'ANG, and WU YING-K'AI. *Chinese Medical Journal [Chin. med. J.]* 81, 207-211, April, 1962. 1 fig., 5 refs.

The authors describe a new method of open-heart surgery they have developed at Tientsin Medical College and Fu Wai Hospital, Peking. The technique is as follows. Hypothermia is induced by surface cooling. Bilateral transverse thoracotomy allows insertion of aortic and caval cannulae. Extracorporeal cooling is added if needed, by oxygenator and heat exchanger. The aorta is occluded below the left subclavian artery, the proximal aorta clamped, and cardiac arrest induced by cold coronary perfusion with acetylcholine. The upper body and head are perfused, and the necessary cardiac operation performed, venting the right ventricle. After cardiectomy the regional perfusion is allowed to become general by releasing the aortic occlusion, and rewarming is started. When the cardiac incision is closed the proximal aortic clamp is removed; the heart's beat begins with perfusion of warm blood, fibrillation being treated by electric shock if necessary.

With this technique 32 operations have been performed. In 21 complicated procedures, such as repair of Fallot's tetralogy, there were 8 deaths, some due to technical defects; others to pulmonary complications. Priming blood requirement did not exceed 1,200 ml. In cyanotic patients hilar collaterals were abundant, but blood loss was minimal. Inadequate blood replacement in earlier cases led to hypotension, but later this was avoided. Serious changes in blood chemistry were not observed.

Advantages of the technique include a dry cardiac field, sparing of the brain, and prompt resuscitation. There is some danger of renal and intestinal damage, thought to be due to venous stasis.

M. Meredith Brown

785. Surgical Treatment of Tetralogy of Fallot

R. ROBERTSON, P. G. ASHMORE, P. ALLEN, and W. B. LEACH. *Journal of Thoracic and Cardiovascular Surgery [J. thorac. cardiovasc. Surg.]* 43, 343-353, March, 1962. 5 figs., 29 refs.

This is a report of 31 cases of the tetralogy of Fallot treated by open-heart operation at the General Hospital, Vancouver.

Shunt operations for the tetralogy of Fallot have a low operative mortality and give good palliative results, but in most cases do not permit full activity. The shunt may be outgrown, with resultant return of dyspnoea and cyanosis.

Open-heart surgery is badly tolerated by infants and a shunt operation is therefore still advocated in children under the age of 2 years; and in older children in whom angiocardio-graphy has revealed a small pulmonary artery. This preliminary shunt operation may relieve the cyanosis and result in enlargement of the pulmonary artery and development of the left ventricle, thus making open correction of the tetralogy possible at a later date. The Blalock anastomosis is preferred because it is easier to close at the time of open-heart repair.

Of the 31 patients described here, 23 were cyanotic and 8 acyanotic; 10 cases were complicated by other lesions or previous operations. Approach was by median sternotomy, and it is stressed that if the shunt is taken down, total correction of the tetralogy must be accomplished immediately if the patient is to survive. Potassium arrest was used in the early cases, but was responsible for 4 deaths from focal necrosis of the myocardium and was therefore abandoned in favour of cold arrest. Ventricular septal defects were closed with an "ivalon" patch and the pulmonary stenosis dealt with by infundibulectomy or enlargement of the pulmonary artery with an ivalon patch, according to its type. Complete removal of the obstruction to the outflow tract without repair of the ventricular septal defect may cause fatal pulmonary congestion. Special care was taken over haemostasis as bleeding is particularly common after open-heart surgery. If postoperative haemorrhage is massive or persistent, thoracotomy should be performed without delay. There were 13 postoperative deaths (6 in complicated cases). As experience has been gained the hazards of the operation have been recognized and avoided, and the operative mortality has fallen. A footnote states that, since the paper was submitted, 10 additional cases (7 of them complicated) have been operated on without a death. The survivors of a good repair are almost invariably able to undertake full activity.

F. J. Sambrook Gowar

786. Familial Aspects of Congenital Heart Disease

C. J. CHELIUS, G. G. ROWE, and C. W. CRUMPTON. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 508-514, April, 1962. 20 figs., 29 refs.

Nineteen families with 2 or more cases of congenital heart disease have been presented. It is concluded that hereditary factors play a role in the etiology of congenital heart disease, but their relative importance remains to be determined. In some families the incidence of congenital heart disease is very impressive.—[Authors' summary.]

787. Atrial Septal Defect. Familial Occurrence in Four Generations of One Family

H. S. ZUCKERMAN, G. H. ZUCKERMAN, R. E. MAMMEN, and M. WASSERMIL. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 515-520, April, 1962. 3 figs., 18 refs.

Eight cases of atrial septal defect occurring in 4 generations of one family are presented. An analysis of the pedigree reveals that the inheritance of the defect is best explained on the basis of transmission of a dominant autosomal gene with incomplete penetrance.

An additional instance of atrial septal defect in the above family was discovered after the completion of this paper. MRC II-4 [a female member of the second generation] had a 34-year-old son, who submitted to surgery for closure of an atrial septal defect at the Minneapolis Veterans Administra-

tion Hospital on September 19, 1961. No other details of the surgical procedure are available to us at the present time. This makes a total of 9 proven and one suspected case of atrial septal defect in this family.—[Authors' summary and addendum.]

VALVULAR DISEASE

788. Anticoagulant Agents in the Surgical Treatment of Mitral Stenosis

L. MISCALL, R. B. NOLAN, A. GORDON, and H. I. MILLER. *Journal of Thoracic and Cardiovascular Surgery* [J. thorac. cardiovasc. Surg.] 43, 382-387, March, 1962. 5 refs.

One of the major hazards of mitral valvotomy is thromboembolism. Attempts to prevent it by the use of anticoagulant drugs are described in this paper from Cornell Medical Center, New York. The operation was performed on 70 patients in 1957; 35 patients were given preoperative anticoagulant therapy and 35 received anticoagulant therapy only for a specific postoperative complication. Anticoagulant therapy was begun at least 3 weeks before operation, the prothrombin time being kept at almost twice normal control during the operative period and for 3 weeks or more after operation. In the treated group there was no case of postoperative thromboembolism, but postoperative bleeding occurred in 11 patients; there were 9 cases of postoperative thromboembolism in the untreated group. In the patients operated on in 1958 and 1959, administration of anticoagulants was stopped 36 to 48 hours before operation and enough vitamin K given to restore the prothrombin time to normal on the day of operation. Anticoagulants were resumed 12 to 24 hours after operation, according to the amount of pleural drainage and the prothrombin time. (Both heparin and oral anticoagulants were used, but heparin only until a satisfactory prothrombin level was reached.) On this regimen there were only 3 cases of postoperative bleeding in 48 cases.

In all, 158 patients were operated on in 1957, 1958, and 1959; in 83, anticoagulant treatment was given as a routine before and after operation, while in 75 it was used only for specific postoperative thromboembolic accidents. Although the treated group contained more patients with heart failure, atrial fibrillation, and preoperative thromboembolism, there were only 2 cases of postoperative embolism in this group compared with 20 in the untreated group. A right-sided surgical approach was used more often in the treated than in the untreated group. The authors recommend preoperative and postoperative anticoagulant therapy for all patients undergoing closed mitral valvotomy. Although the open-heart operation has many advantages, it has not eliminated the risk of thromboembolism.

F. J. Sambrook Gowar

789. Deterioration after Mitral Valvotomy

C. P. LOWTHER and R. W. D. TURNER. *British Medical Journal* [Brit. med. J.] 1, 1027-1036, April 14, and 1102-1107, April 21, 1962. 7 figs., 10 refs.

These two papers from the Western General Hospital, Edinburgh, are concerned with the first 500 patients with rheumatic heart disease who were treated by valvotomy for proved severe mitral stenosis during the past 11 years. The over-all operative mortality has remained constant at

between 6 and 7%. Systemic embolism is the chief hazard of the procedure and accounted for 13 of the 31 deaths, while operative mitral incompetence was responsible for 6 of the deaths. Since the introduction of the transventricular dilator there has been a high incidence of systolic murmurs but not of traumatic incompetence of any dynamic significance.

An analysis of the 200 patients operated on in the first 6 years of the period showed that in the first postoperative year 84% maintained a good result. After 5 years the proportion fell to 72% and thereafter deterioration increased by about 10% per annum. At the end of 8 years only 42% had maintained a good result. The numbers with stenosis steadily increased and the proportion requiring a second valvotomy rose from 5% at the end of 5 years to 40% at the end of 7 years; the average interval between operations was 6 to 7 years. The mortality for second operations in 92 cases was 2.4%, but the results of the second operation have appeared to be less good than those of the first. The authors note that subsequent deterioration is sometimes mainly attributable to a single dominant factor, of which stenosis is the most important, and sometimes to a combination of adverse features, such as atrial fibrillation, cardiac enlargement, calcification of the valve, traumatic mitral incompetence, and an age of 50 years or more.

Physical signs of concomitant aortic incompetence were found in 262 patients and of aortic stenosis in 103. Defects of the aortic valve did not affect the operative mortality or the long-term results up to 6 years. Where the degree of stenosis was severe, aortic valvotomy was carried out at the same time. The authors conclude from this analysis that although most patients with severe mitral stenosis are improved by valvotomy, surgical treatment is but an incident in the relentless progress of rheumatic heart disease, whether from activity of the process or from the progressive fibrosis which follows activity.

T. Semple

CORONARY DISEASE AND MYOCARDIAL INFARCTION

790. **The Precordial Accelerogram in Ischemic Heart Disease. A Study of Middle-aged and Old Patients with Angina Pectoris; Recent and Old Myocardial Infarction** L. M. ROSA, J. P. CONSTANTINO, N. KARSAK, R. REICH, and B. ZEEMER. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 534-540, April, 1962. 4 figs., 17 refs.

The precordial acceleration tracings in ischaemic heart disease were studied in 281 patients at Mount Sinai Hospital, Chicago. The tracings were obtained during quiet respiration with the patient in bed or on a table in readiness for routine electrocardiography.

The findings confirmed previous observations on the influence of ischaemic heart disease on the precordial leads during pulsation of the heart. The tracings were abnormal in 93.3% of the 281 cases. Of 117 patients with old and recent myocardial infarction, diastolic abnormalities of the precordial pulse were present in 94.5%, and of this last group 96.5% showed two or more distorted phases in one cardiac cycle. In 66.6% of the patients with a definite anginal syndrome and a normal electrocardiogram the tracings were abnormal and in 53% there was abnormal diastolic pulsation.

The authors state that a correlation of "statistically abnormal" tracings with the individual clinical data was possible by graded classification; in doubtful or borderline cases precordial graphs of acceleration supplemented conventional methods.

Leon Gillis

791. **The Vibrocardiographic Exercise Test for Coronary Insufficiency**

C. M. AGRESS and S. WEGNER. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 541-546, April, 1962. 4 figs., 6 refs.

Experience with the vibrocardiographic exercise test in patients with normal hearts and in those suffering from coronary insufficiency is described in this paper from the University of California and the Veterans Administration Center, Los Angeles. The test is simple to perform and can be carried out in the consulting room, and the tracings give a high degree of correlation with the clinical condition of the patient.

The initial deflections of the vibrocardiogram were measured before and after a single two-step test in a group of 74 subjects, including normal controls and patients with myocardial ischaemia. The normal response was a widening of the wave intervals when they were expressed as a ratio of total systole. The increase ranged from 5% to 200%. In the patients there was a decrease which ranged from 5% to 63%. A borderline response was found to be a change which ranged from +5% to -5%.

The results of this form of exercise test were compared with those of the single two-step test performed simultaneously. Of the group of normal and "functionally normal" subjects there was correlation with the clinical status by the two-step test in 87% and by the vibrocardiographic interval test in 94%. In the patients with coronary insufficiency the correlation was 66% with the two-step test and 88% with the vibrocardiographic test.

Leon Gillis

792. **Radio-iodine in the Management of Refractory Cardiac Pain**

J. A. STRONG and R. W. D. TURNER. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 221-233, April, 1962. 2 figs., 8 refs.

The authors, from the Western General Hospital, Edinburgh, describe the use of radioactive iodine (^{131}I) as a treatment for intractable cardiac pain in 29 patients (18 males and 11 females) aged from 35 to 72 years. Of these, 21 had clinical and electrocardiographic evidence of coronary arterial disease and 8 had physical signs of severe aortic valvular disease with considerable left ventricular hypertrophy. No patient had recently suffered a myocardial infarction. The patients were assessed clinically in hospital, and special investigations included serial estimations of blood cholesterol level and a ^{131}I test of thyroid function. The therapeutic dose of ^{131}I was ultimately standardized at 25 mc. irrespective of data obtained from pretreatment tests.

Follow-up reports extend from a minimum of 13 months to 6 years. Six patients died within 4 months of treatment, 3 from myocardial infarction and 3 from severe aortic disease, and are excluded from the analysis of results. Of the remaining 23 patients, 20 considered they had benefited from the treatment with respect to relief from pain and

increased exercise tolerance. In 18 patients with coronary arterial disease hypothyroidism developed, and only 2 did not derive some benefit. Of these 18, however, 11 subsequently died from myocardial infarction or congestive cardiac failure, including 9 who had a "good" or "fairly good" result. All 5 patients with aortic valvular disease had a "fair" result for 5 or more years, one patient dying after 5 years. Although relief from pain was striking in a few cases, it was often of limited degree and duration and was unrelated to the results of the ^{131}I studies before or after treatment. The greatest relief was seen in excitable patients, presumably because of increased emotional stability and/or a change in their pain threshold.

The average increase in blood cholesterol level after treatment was 134 mg. per 100 ml., but no evidence of increased atheroma formation or of myxoedema heart disease was found. The authors consider that the advantages of this simple method of treatment are such as to render it the first recourse after conventional vasodilators had failed, and that it is superior to surgical methods of interrupting sensory pathways.

J. Warwick Buckler

793. The Significance of Prolonged Anginal Pain (Preinfarction Angina)

W. H. RESNIK. *American Heart Journal* [Amer. Heart J.] 63, 290-298, March, 1962. 4 figs., 18 refs.

When anginal pain continues for more than 15 minutes the question of the presence of an underlying coronary thrombosis arises. The differentiation between a coronary thrombosis and such a prolonged attack of angina may be difficult: the author considers a rise in serial serum transaminase levels to be the most reliable single index of the presence of myocardial necrosis. He now reports observations made at Stamford Hospital, Stamford, Connecticut, on 31 cases of prolonged anginal pain in which serum glutamic-oxalacetic transaminase (S.G.O.T.) activity was estimated. Levels of under 40 units in cases without other signs of infarction were considered to be due to prolonged angina. In 23 cases the peak levels of S.G.O.T. did not occur till 4 to 10 days after the occurrence of symptoms—probably, the author suggests, because of slow necrosis of very small areas of myocardium. Discussing the importance of this finding, he concludes that it is safer to give anticoagulant therapy promptly to all patients with prolonged angina.

J. B. Wilson

794. Cardiac Infarction in Early Middle Age. (Der Herzinfarkt im jüngeren Erwachsenenalter)

K. H. STRAUPE. *Zeitschrift für die gesamte innere Medizin und ihre Grenzgebiete* [Z. ges. inn. Med.] 17, 285-293, April 1, 1962. 42 refs.

From the Medical Clinic of the University of Rostock the author reports 33 cases, collected from 6 hospitals, in which coronary occlusion occurred before the age of 40. Of these patients 30 were males, the youngest being aged 28, and 3 were females, of whom the youngest was 35. The site of the infarct was anterior in 19, posterior in 12, and lateral in 2. Coronary sclerosis was severe in 6 of the 9 for whom post-mortem reports were available. Exhaustive family histories of 27 of these patients revealed that in two-thirds of them cardiovascular disease, obesity, diabetes mellitus, and gout were present in blood relatives. None of the 33 patients suffered from diabetes, but hypertension (blood

pressure 160/100 mm. Hg) was found in 7 men and one woman, and obesity in 10 men and 2 women. All the female patients as well as 15 males worked predominantly in sedentary occupations, the remaining 15 men being manual workers. Stress was an important aetiological factor in 18 of 29 patients. Of 31 patients, one woman smoked very heavily (over 40 cigarettes daily), 12 men smoked heavily (20 to 40 daily), 13 men and 2 women smoked moderately (10 to 20 daily), and 3 men smoked under 10 cigarettes a day. Twelve of the 33 patients had suffered from relatively mild anginal attacks for weeks or months before infarction occurred, while 9 had complained of vague pains misdiagnosed as "rheumatism", but the remaining 12 had had no prodromal symptoms at all. The infarction had occurred on waking in 6 cases, at rest, often after a meal, in 7, within the framework of their ordinary activities in 12, following trauma of the chest wall in one, and after unusual effort in 4. Severe, continuous cardiac pain was the presenting symptom in 19 patients, while in 9 the pain was moderately severe. In 3 cases of posterior infarction there was atypical distribution of the pain, and in one patient infarction was painless.

The author stresses that the possibility of myocardial infarction in younger patients must be borne in mind, since it may occur without previous cardiac pain or any undue exertion. In 5 of his cases it was discovered only after electrocardiographic investigation and in 4 post mortem. He believes that both the short-term and long-term prognosis is more favourable in patients under 40 than in those over 60. Of the present 33 patients 6 were dead within 8 weeks of the attack, but 26 survived for one year after it. Of 21 patients who survived 6 months only one remained a permanent invalid, 14 being able to return to their former employment, 3 others to similar but easier work, and 3 had to change their employment for something less exacting.

E. S. Wyder

BLOOD VESSELS

795. Fifty-three Cases of Coarctation of the Aorta

R. R. MARTELLE and A. J. MOSS. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 103, 556-563, April, 1962. 1 fig., 14 refs.

The authors have analysed the records of all cases of coarctation of the aorta treated at the University of California Medical Center, Los Angeles, from 1955 to 1959. During this period 53 children with this abnormality were admitted; there were 29 males and 24 females, 30 of them under the age of one year. Signs and symptoms are listed. Of the 53 cases, 26 were asymptomatic; in most of these the diagnosis was made after the first year of life, whereas of the 27 cases with symptoms 23 were diagnosed in the first year. A cardiac murmur was present in 48 cases, and the 32 cases in which this was the only cardiac abnormality were analysed. The murmur was most commonly soft and loudest in the 2nd left intercostal space; the next most common situation was in the 1st and 2nd right intercostal spaces. In 20 cases it radiated to the back. [No details of timing are given.] Diminished femoral pulsation was noted in 38 cases, but suprasternal pulsation in only one case. The blood-pressure gradient between the upper and lower extremities varied between 0 and 145 mm. Hg, but the level of systemic pressures is not given. Alterations in the pressure gradient

following operation are illustrated graphically in 30 cases. Congestive cardiac failure occurred in 47% of infants, but not after the age of one year. Headaches were complained of by 5 patients; leg pains by only 3.

The electrocardiogram in infancy showed either right ventricular hypertrophy or combined right and left hypertrophy. Over the age of one year left ventricular hypertrophy was commoner, but in 14 of the 24 cases in this age group the electrocardiogram was normal. Radiographs showed enlargement of the heart in patients under one year of age, but 67% of these had associated cardiac abnormalities, whereas these were present in only 17% of those over this age. The commonest associated cardiac abnormality was patent ductus arteriosus, occurring in 14 out of 30 patients under one year old; the next commonest was ventricular septal defect (5 out of 30 under one year). Other cardiac defects, which were much rarer, are listed. Extra-cardiac abnormalities were uncommon, affecting only 6 cases, respectively cleft palate, cataract, macrocephaly, epilepsy, multiple neurofibromatosis, and Turner's syndrome.

The authors give details of operative treatment. There were 9 deaths (4 operative, 5 medical)—an over-all mortality of 17%. On 13 patients under the age of one year resection with end-to-end anastomosis was performed, with 4 deaths. A similar operation was undertaken without mortality in 30 patients over the age of one year. Operative complications are described.

The authors prefer operative treatment to medical management in infants with congestive cardiac failure, extreme hypertension, or cardiomegaly.

H. G. Farquhar

796. On the Question of Arterial Hypertension in Coarctation of the Aorta. (К вопросу о повышении артериального давления при коарктации аорты) N. N. VYSOCKIJ and G. M. MEL'NIKOVA. *Терапевтический Архив* [Ter. Arkh.] 34, 76-78, April, 1962.

Until quite recently the arterial hypertension which occurs in patients with coarctation of the aorta was thought to be due exclusively to the mechanical factor, that is, the focal narrowing of the aorta. Some authors, however, now consider that the increased systolic pressure in this condition is mechanical and the diastolic humoral. As a contribution to this problem the present authors describe the behaviour of the blood pressure in a case of coarctation before and after resection of the affected segment of the aorta and its subsequent replacement by a "dapron" graft. Before the operation in May, 1960, the arterial pressures in the right and left arms were 210/70 and 160/80 mm. Hg respectively and in the legs 100/70 and 110/85 mm. Hg respectively. At operation, performed in September, 1960, a graft 10 cm. long was inserted. When the patient was discharged the arterial pressures in the limbs were about the same as before operation. In May, 1961, however, the mean arterial pressure in the arms had risen to 190/117 mm. Hg and in the legs to 185/112 mm. Hg; thus 8 months after surgical repair of the coarctation the hypertension had become general.

In the authors' opinion it must be assumed that in this case two factors were concerned in the hypertension, a neurogenic factor and a mechanical factor. Since the mechanical factor was removed it is argued that the continued high pressure must now be due exclusively to the

neurogenic factor. Further, this latter factor cannot be purely functional, but is probably partly morphological, since before the operation this patient had symptoms of encephalopathy, probably due to a raised intracerebral pressure. H. W. Swann

797. A Hypothesis to Explain the Accumulation of Cholesterol in Atherosclerosis

C. W. M. ADAMS, O. B. BAYLISS, and M. Z. IBRAHIM. *Lancet* [Lancet] 1, 890-892, April 28, 1962. 6 figs., 4 refs.

In this preliminary communication from Guy's Hospital Medical School, London, the authors report that histochemical studies have shown that the activity of most enzymes of the normal and atherosclerotic aortic wall diminishes progressively in the ageing and atherosclerotic vessel. Thus the decrease in such activity is first observed in the middle zone of the media, but with an increasing degree of atherosclerosis enzyme activity diminishes also in the inner zone of the media; in the outer part of the media, however, some enzyme activity is maintained even in severe atherosclerosis. Since the inner part of the media is nourished by direct permeation from the lumen of the artery while the outer part is supplied by the vasa vasorum, it would be reasonable to attribute the loss of enzyme activity observed in the inner part of the media in aged or atherosclerotic subjects to ageing of the arterial wall.

In experimental studies, when adult Wistar rats were injected intraperitoneally with tritium-labelled cholesterol, autoradiographs of sections of the intima obtained 8 hours after the injection showed that the injected material was accumulated solely in the intima. Autoradiographs obtained 27 hours after injection or later, however, showed the injected material concentrated not only in the intima but also in the inner and middle third of the media. The fact that there is a higher concentration in the inner third than in the middle third of the media seems to indicate that the labelled cholesterol migrates through the wall by routes other than via the vasa vasorum, and the direction is from the lumen outwards. The authors add that further studies are in progress to support their tentative hypothesis that enzyme defects of the ageing anoxic media restrict the migration of cholesterol from the intima, thus leading to an accumulation of the substance in the internal part of the arterial wall. Z. A. Leitner

798. Superficial Thrombophlebitis of the Chest Wall

W. C. JOHNSON, R. WALLRICH, and E. B. HELWIG. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 103-108, April 14, 1962. 5 figs., 30 refs.

The clinical and pathological findings in 7 patients (2 male and 5 female, aged 25 to 39 years) with superficial thrombophlebitis of the chest wall (Mondor's disease) are described in this paper from the Armed Forces Institute of Pathology, Washington. Presenting clinical features included pain, tenderness (particularly with body movement), and a subcutaneous cord, all in the area bounded by the anterior axillary line or breast and the lower costal margin or umbilicus. There was no clinical or laboratory evidence of systemic disturbance. The pain and tenderness lasted up to 6 weeks, while a palpable cord persisted up to 7 months. One patient was given antibiotics, but this treatment did not influence the course of the condition as compared with the other patients given no specific therapy.

Examination of biopsy specimens, obtained from all the patients, revealed that the involved structures were small veins between the corium and subcutaneous tissues. There were four pathological stages—an initial thrombosis, organization of the thrombus, recanalization, and finally a residual recanalized vein with thickened fibrous walls. These four phases lasted from 2 to more than 24 weeks.

The literature on this condition is briefly reviewed and the aetiology discussed. The authors conclude that mechanical injury to the veins, either directly or as a result of exertion or surgical procedure, is the predominant causative factor and results in mild inflammatory thrombosis with eventual recanalization. Although the condition may be confused with lymphatic spread of carcinoma, neoplasia has no part in the aetiology. *Gerald Sandler*

799. Microscopic Observations of the Bulbar Conjunctival Vessels in Rheumatic Disease in Children

T. NAKAO and T. NITTA. *Tohoku Journal of Experimental Medicine [Tohoku J. exp. Med.]* 75, 341-345, Jan. 25 [received May], 1962. 5 figs., 4 refs.

Slit-lamp examination of the temporal bulbar conjunctiva in children with rheumatic fever at Aomori Prefectural Central Hospital, Japan, revealed a characteristic pattern consisting in repeated subdivision (arborization) and abrupt thinning of many terminal vessels. This feature was present in 10 out of 18 patients with rheumatic disease, but in only 2 out of 17 with non-rheumatic diseases who acted as controls. The authors state that the phenomenon is not pathognomonic of rheumatic disease. *John Lorber*

HYPERTENSION

800. Methyldopa in Hypertension: Clinical and Pharmacological Studies

C. T. DOLLERY and M. HARRINGTON. *Lancet [Lancet]* 1, 759-763, April 14, 1962. 7 figs., 7 refs.

The action of methyldopa in interfering with the formation of serotonin and noradrenaline in the body led to the introduction of its L-isomer, in which its biological activity has been shown entirely to reside, in the treatment of patients with hypertension. Tests at Hammersmith Hospital (Postgraduate Medical School), London, showed that after a single oral dose of 2 to 4 g. of methyldopa a hypotensive effect appeared in 4 to 5 hours and persisted for 24 hours. Studies with ^{14}C -labelled methyldopa revealed that the drug was well absorbed by mouth and that about one-half of the dose appeared in the urine within 24 hours. After intravenous injection the drug was fully excreted in the urine provided renal function was normal, but uraemic patients excreted only a fraction of the dose.

In the main study 59 patients with hypertension were treated with methyldopa ("aldomet") by mouth in a daily dose of 0.5 to 4 g. Satisfactory control of the blood pressure, defined as a maintained pressure of less than 160/100 mm. Hg, was achieved in 32 of these. In successful cases the blood pressure fell in both the upright and lying positions. The additional postural effect was slight, and exercise had little influence on the hypotensive effect. In regard to side-effects, drowsiness occurred initially in almost all patients, and nasal stuffiness and dry mouth were also sometimes complained of. Of the 27 patients in whom treatment with

methyldopa was unsuccessful, 10 who had mild or moderate hypertension had to be maintained on less than adequate doses to avoid side-effects. In a further 7 patients the drug was abandoned because it exerted no hypotensive effect in maximum dosage, and in 7 others treatment was complicated by the development of severe fluid retention, although this was controlled with chlorothiazide in 3 cases. In the remaining cases treatment was stopped because of cerebral or myocardial ischaemia or increasing uraemia.

The authors point out that control of the blood pressure with methyldopa tended to be less successful in the more severe cases, particularly in younger males. Some degree of tolerance to the drug developed in a few cases after prolonged treatment. They conclude that methyldopa will occupy a place in the management of hypertension intermediate between that of the milder hypotensive drugs, such as reserpine, and the more potent ones, such as guanethidine. They do not recommend methyldopa as the drug of first choice in the treatment of the more severe grades of hypertension. *Bernard Isaacs*

801. The Significance of α -Methyldopa in the Treatment of Chronic Hypertension. (Die Bedeutung des α -Methyldopa für die Behandlung der chronischen Hypertonie)

O. H. ARNOLD. *Deutsche medizinische Wochenschrift [Dtsch. med. Wschr.]* 87, 844-848, April 27, 1962. 32 refs.

L- α -Methyl-3:4-dihydroxyphenylalanine (α -methyldopa) probably acts by antagonizing the decarboxylation of dihydroxyphenylalanine and 5-hydroxytryptophan to noradrenaline and 5-hydroxytryptamine respectively. At the Essen City Hospital α -methyldopa was tried in combination with a thiazide diuretic in the treatment of 41 patients with chronic arterial hypertension of varied aetiology. In more than half these patients the diastolic blood pressure was over 120 mm. Hg. Duration of treatment varied from 1 to 8 months. The results, which are tabulated, show falls in the resting diastolic pressure ranging from 10 to 50 mm. Hg. The effect of the drug was greater than that of a combination of reserpine and thiazide in equivalent doses, but less than that obtained with guanethidine and thiazide. The particular advantage of α -methyldopa is that it caused no complications or side-effects. Its disadvantages were poor absorption after oral administration, brevity of action, expense, and possible development of tolerance. *D. Goldman*

802. Bretylium Tosylate in Treatment of Severe Hypertension

K. SOMERS. *British Medical Journal [Brit. med. J.]* 1, 911-913, March 31, 1962. 20 refs.

The author reports from Makerere University College, Uganda, his experience in treating 29 hypertensive patients with bretylium tosylate. Satisfactory control of the blood pressure was obtained (160/100 mm. Hg or less on standing) in 14, but control was unsatisfactory in 15. Dizziness and muscular weakness were common side-effects. Tolerance to the drug developed in some patients and treatment was usually altered when the dose reached 3.6 g. daily, although one patient was resistant to 18.6 g. daily. The author comments that the high incidence of unsatisfactory response makes bretylium tosylate unsuitable for initial management of hypertension or for long-term management of severe hypertension. *C. T. Dollery*

Clinical Haematology

803. **The Relationship between Polycythaemia Vera and Chronic Myelosis.** (О взаимосвязи между истинной полицитемией и хроническим миелозом)
S. I. ŠERMAN and L. M. ROZANOVA. *Терапевтический Архив [Ter. Arkh.]* 34, 99-104, March, 1962. 26 refs.

Polycythaemia vera often ends in chronic myelosis or in myelofibrosis. It has been suggested by some authors that this is due to the effect of irradiation given in treatment and is not the normal outcome of the disease. To test this theory the authors studied 75 patients with polycythaemia vera (50 women and 25 men) who had had the disease for periods ranging from 5 to 17 years, and who had been under observation from the beginning of 1952 to the middle of 1961. During these 9½ years 7 of the patients died; of the remainder, 35 (50%) gradually developed the typical picture of transition to chronic myelosis. Of these, 11 had never received irradiation. The authors suggest that the irradiated patients lived longer because of less tendency to thrombosis, having been treated with radioactive phosphorus and anticoagulants and by blood-letting. This combined treatment in their opinion gives the best results, prolonging not only life but ability to work, by retarding the progress of the disease and preventing complications from thrombosis in vital organs. In their view the transition to chronic myelosis and myelofibrosis is a tendency in all patients with this disease who live long enough, and is therefore naturally more frequent in those whose life has been prolonged by treatment, including that with radioactive phosphorus.

L. Firman-Edwards

804. **Haemorrhagic Thrombocythaemia and Its Treatment with Radioactive Phosphorus**

J. R. FOUNTAIN and M. S. LOSOWSKY. *Quarterly Journal of Medicine [Quart. J. Med.]* 31, 207-220, April, 1962. 2 figs., 47 refs.

In this paper from the General Infirmary at Leeds the authors give an account of the clinical and laboratory findings in 9 cases of haemorrhagic thrombocythaemia. These patients all had a bleeding diathesis and assessment of their haemostatic mechanisms revealed an increase in the platelet count, usually to over 1 million per c.mm., as the important finding. Detailed clinical descriptions of these cases are given. The patients (6 males and 3 females) were aged between 30 and 74 years. Splenomegaly was present in 5 cases, and in 2 splenectomy had been performed. Leucocytosis was a frequent accompanying feature. Gastro-intestinal haemorrhage was a particularly common manifestation. The authors conclude that this condition belongs to the group of myeloproliferative disorders, and that defective splenic function is important in the aetiology of some cases. The fundamental explanation of the mechanism of the bleeding, however, remains uncertain.

The treatment used was repeated intravenous injections of radioactive phosphorus usually in a dose of 3 or 4 mc. No toxic effects were noted. When the platelet count fell below 500,000 per c.mm. there was cessation of abnormal bleeding.

A. S. Douglas

ANAEMIA

805. **Primary or Essential Sideroachrestic Anaemias: Pathogenesis and Therapy.** [In English]

M. C. VERLOOP, M. BIERENGA, and A. DIEZERAAD-NJOO. *Acta haematologica [Acta haemat. (Basel)]* 27, 129-145, 1962. 6 figs., 30 refs.

The term sideroachrestic anaemia is used to describe an iron-deficiency anaemia which is due to the non-utilization of iron although adequate and available amounts of the element are present. The blood presents a hypochromic picture, but the serum iron level is normal or high. However, the incorporation of intravenously injected labelled iron into the erythrocytes is much below normal, much of the iron disappearing into the liver. Many of these cases are secondary, that is, the poor iron utilization is part of a pernicious anaemia or other syndrome.

But some cases occur that do not fit into any other syndrome, and these are the primary or essential cases. In this paper from the University Medical Clinic, Utrecht, the authors divide the primary cases into a familial hypochromic form and an isochromic or even hyperchromic form which occurs in patients aged over 50 and which seems to be acquired. The results of a large number of haematological tests are presented, but no very clear pattern emerges apart from the features already mentioned and the fact that most cases are refractory to all forms of treatment. Three of the authors' cases responded incompletely to pyridoxine and these should be classed with the pyridoxine-resistant anaemias; one patient responded, surprisingly, to vitamin C. The authors also point out that the isochromic acquired type may be difficult to distinguish from the more chronic form of Di Guglielmo's erythraemia. Haemochromatosis was found in 2 patients aged 50 and 83 respectively. Sideroblasts, that is, iron-containing normoblasts, were found in the marrow of all the patients.

M. C. G. Israëls

806. **Two Cases of Aplastic Anaemia Associated with Tumours of the Thymus**

R. D. S. BARNES and P. O'GORMAN. *Journal of Clinical Pathology [J. clin. Path.]* 15, 264-268, May, 1962. 4 figs., 25 refs.

807. **Haemorrhage Associated with Thrombocytopenia in Megaloblastic Anaemia**

M. D. SMITH, D. A. SMITH, and M. FLETCHER. *British Medical Journal [Brit. med. J.]* 1, 982-985, April 7, 1962. 12 refs.

Although reduction in the platelet count is common in megaloblastic anaemia, thrombocytopenia sufficiently severe to cause haemorrhage is uncommon. This paper, from the Royal Infirmary, Glasgow, gives details of 9 patients suffering from megaloblastic anaemia in whom this complication occurred. The megaloblastic anaemia was due to pernicious anaemia in 4 patients, pregnancy in 3, malabsorption syndrome in one, and administration of primidone in one. In 5 patients the platelet count was below 20,000 per c.mm., the lowest count recorded being 5,000 per c.mm.

The haemorrhagic manifestations, which were severe, included epistaxis, haematemesis and melaena, haematuria, menorrhagia, and skin lesions. In all except one patient, in whom there was a delayed response, the platelet count rose promptly to normal after the appropriate haematinic had been given, although some patients were given steroids also. The authors state that the thrombocytopenia is part of the dyshaematopoietic state produced by deficiency of cyanocobalamin (vitamin B₁₂) or folic acid.

J. L. Markson

808. Blocking of Maturation of the Erythroblastic Series in Haemolytic Anaemia. Clinical and Karyometric Study. (Le blocage de maturation de la série érythroblastique au cours des anémies hémolytiques. Étude clinique et caryométrique)

G. MARCHAL, A. GOUTTAS, G. BILSKI-PASQUIER, H. TSEVERENIS, G. DUHAMEL, N. VORIAS, A. PAPASPYROU, and A. FERTAKIS. *Semaine des hôpitaux de Paris* [*Sem. Hôp. Paris*] **38**, 1039-1047, March 26, 1962. 18 figs., 37 refs.

At the Hôpital Broussais, Paris, 10 cases of haemolytic anaemia have been studied during crises attributable to maturation arrest in the erythrocyte precursors. They included 3 cases of thalassaemia, 2 of congenital spherocytosis, 2 of congenital non-spherocytic haemolytic anaemia, 2 of acquired haemolytic anaemia with cold antibodies, and one of symptomatic haemolytic anaemia occurring in the course of chronic lymphatic leukaemia. In all 10 cases maturation arrest was manifested in the peripheral blood by exacerbation of the anaemia with reticulocytopenia. The aetiology of this complication is uncertain and probably differs from case to case. As regards the suggestion of Dameshek and Bloom (*Blood*, 1948, **3**, 138) that maturation arrest may be a consequence of "hypersplenism", it is of interest that in the 2 cases of congenital non-spherocytic haemolytic anaemia in the series maturation arrest followed 10 and 12 days respectively after splenectomy. The duration of maturation arrest is generally 2 to 3 weeks, but in one of the present cases it lasted for 10 weeks and in another for 6 months. In the former case the complication later recurred, although remission of maturation arrest is generally spontaneous and complete.

In the present study serial observations were made on the bone marrow and marrow samples were subjected to the karyometric procedure of Jacoby (*Wilhelm Roux Arch. Entwickl.-Mech. Org.*, 1925, **106**, 124; 1941, **141**, 584). The marrow showed typical erythroblastopenia in 4 cases, but in 4 cases the number of erythrocyte precursors was increased and the appearances resembled those of megaloblastic erythropoiesis. The authors believe that karyometric observations provide an explanation for the mechanism of maturation arrest and also enable cases which simulate megaloblastic erythropoiesis to be distinguished from cases of true megaloblastic erythropoiesis. A. G. Baikie

809. The Treatment of Autoimmune Hemolytic Anemia with 6-Mercaptopurine and Thioguanine

R. SCHWARTZ and W. DAMESHEK. *Blood* [*Blood*] **19**, 483-500, April, 1962. 5 figs., 37 refs.

The use of cytotoxic substances in the treatment of autoimmune haemolytic anaemia was suggested by the known beneficial effects of corticosteroids and the possibility that these effects were due to some interference with antibody

production. It has previously been shown by the authors (*J. clin. Invest.*, 1959, **38**, 1394) that 6-mercaptopurine could depress immune responses in some experimental animals. At the Pratt Diagnostic Clinic-New England Center Hospital, Boston, 14 patients with autoimmune haemolytic anaemia were treated with either 6-mercaptopurine or an analogue, thioguanine. In all the patients the usual features of haemolytic anaemia were present and the response to the direct Coombs test was positive. One patient had chronic lymphatic leukaemia and 2 had disseminated lupus erythematosus, while the latter disease was suspected in one other patient. In the remaining patients the haemolytic anaemia was apparently idiopathic. Thioguanine was given to 11 patients and 6-mercaptopurine to 3, the dosage of each drug being 2.5 mg. per kg. body weight daily.

A satisfactory therapeutic response was obtained in 9 patients and this was sustained with or without maintenance therapy in 6. Of the 5 patients in whom treatment was considered to have failed, one responded satisfactorily to thioguanine but treatment was stopped because of toxic effects on the bone marrow and the gastro-intestinal tract. Corticosteroids had been given previously to 9 of the patients and that treatment was considered to have failed or had to be discontinued because of side-effects. Of these 9 patients the response to the cytotoxic drug was regarded as satisfactory in 4, partial in one, and unsatisfactory in 4. Cytotoxic agents only were given to 2 of the 14 patients and both responded well—one to thioguanine and one to 6-mercaptopurine; neither of these patients required maintenance therapy.

Toxic effects on the bone marrow were observed in 3 patients and were considered to be transient in 2 of them. In 2 patients dyspeptic symptoms developed which called for cessation of treatment. No difference was noted in toxic or other effects between thioguanine and 6-mercaptopurine. In all patients who responded a fall in the reticulocyte count was associated with decreased bilirubinaemia and, later, a rise in the haemoglobin level. The response to the direct Coombs test continued to be positive in all the patients except one, although the titres were reduced in the others.

The authors suggest that the eventual place of these two drugs in the treatment of acquired haemolytic anaemia has not yet been clearly established. A. G. Baikie

810. Postsplenectomy Infection in Cooley's Anemia: an Appraisal of the Problem in This and Other Blood Disorders, with a Consideration of Prophylaxis

C. H. SMITH, M. E. ERLANDSON, G. STERN, and M. W. HILGARTNER. *New England Journal of Medicine* [*New Engl. J. Med.*] **266**, 737-743, April 12, 1962. 34 refs.

This discussion on the danger of severe or fatal infections following splenectomy in children suffering from thalassaemia major (Cooley's anaemia), with some special reference to the age of the patients in whom the operation is performed, comes from New York Hospital-Cornell Medical Center, New York. The authors refer to their earlier paper (*Amer. J. Med.*, 1957, **22**, 390) dealing with severe and fulminating infections after splenectomy in childhood for a variety of haematological diseases, and the present paper confirms their view that removal of the spleen in childhood does influence susceptibility to infection. They now report that, of 33 children subjected to splenectomy for severe

Cooley's anaemia, 7 suffered within 2 years from severe infections and 5 died. This contrasts with 23 children suffering from the same disease but not treated by splenectomy, of whom 3 had severe infections but none died. Pneumococcal septicaemia or meningitis was the chief infection, with *Escherichia coli* infections next in number, but other micro-organisms may also be involved. They point out that age at operation is of importance—the younger the child, the greater the risk, this being especially true in the first year of life.

The authors discuss fully the problem, raised for many years but never adequately solved, of how important the spleen with its great content of reticulo-endothelial (R.E.) cells really is in dealing with invading micro-organisms. It must be pointed out, however, that R.E. cells are abundant elsewhere, notably in the bone marrow, liver, lungs, and lymph nodes. They also admit that most, if not all, of the children involved had received numerous blood transfusions to combat the haemolysis and anaemia characteristic of the disease, and that in consequence large deposits of haemosiderin may have occurred which might block or partly block R.E. cells wherever they are found in the body.

Finally, the question of possible prophylaxis is carefully examined. In all their recent cases the authors have given antibiotics (tetracycline, 250 mg., or penicillin, 200,000 units daily) as a routine for 2 years after splenectomy. At present they have 17 patients in their clinic suffering from Cooley's anaemia in whom splenectomy has been performed. Of these, 8 are still receiving antibiotics and 3 have completed the 2-year course. There has been one fatal infection in the antibiotic group, due to *Esch. coli*. They conclude that prophylaxis against Gram-negative invaders is at the present time generally unsuccessful, since these organisms rapidly became resistant. *J. W. McNee*

NEOPLASTIC DISEASES

811. Anaemia in the Reticuloses

A. J. BOWDLER and T. A. J. PRANKERD. *British Medical Journal* [Brit. med. J.] 1, 1169–1175, April 28, 1962. 6 figs., 34 refs.

One of the most constant features of the reticuloses is the appearance of anaemia at some stage, and in this paper from University College Hospital and Medical School, London, the aetiology and management of this anaemia are discussed.

Haemorrhage is a major factor in the causation of anaemia in a minority of patients only and is often associated with a low platelet count. There is now ample evidence that the erythrocyte life span may be shortened in some patients with reticuloses, and autoimmune haemolysis has been demonstrated in chronic lymphatic leukaemia, lymphosarcoma, Hodgkin's disease, and reticulosarcoma, while latent haemolytic anaemia possibly of extracorporeal causation has been described in a substantial number of the more common reticuloses. At present the most useful division of cases is as follows: (1) those in which there is no dominant organ responsible for destruction and (2) those in which one organ, usually the spleen, is playing a significant part.

Although, in general, the anaemia accompanying reticulosis is due to reduced erythrocyte production, which previ-

ously was considered to be the result of marrow replacement, there is now evidence that impairment of erythrocyte production may be associated with an inadequate response to the demands of the usual controlling factors. Commonly, a combination of both increased erythrocyte destruction and marrow suppression is present. Other forms of anaemia, such as idiopathic hypochromic anaemia and folic-acid deficiency, have also been found in association with the reticuloses. Most of the anaemias are normocytic and normochromic.

Satisfactory treatment must depend on a correct diagnosis which may be established by radioactive isotope procedures. Replacement of blood loss and suppression of the lymphomatous process may temporarily alleviate the anaemia, while steroid therapy is often effective, not only in cases associated with haemolytic anaemia. Occasionally splenectomy may be of value. *A. Ackroyd*

812. Study of 50 Cases of Acute Leukaemia in Childhood

R. B. THOMPSON and W. WALKER. *British Medical Journal* [Brit. med. J.] 1, 1165–1169, April 28, 1962. 3 figs., 10 refs.

A study is reported of 50 consecutive cases of acute leukaemia admitted to the Royal Victoria Infirmary, Newcastle upon Tyne, between 1953 and 1960. The patients (30 male and 20 female), all of whom died, were observed during most of the illness. The youngest patient was 5 weeks old and the oldest was 14 years; the peak incidence of the disease occurred in the age group 2 to 4 years.

The principal presenting symptoms were pallor and general ill-health, bruising and haemorrhage, lymphadenopathy, fever, bone pain, skin infiltration, and proptosis, in that order. The clinical findings on first examination included anaemia in all except one of the patients, skin haemorrhages in 37, generalized lymph-node enlargement in two-thirds, and enlargement of the spleen and of the liver in 44 and 42 patients respectively. Fever was present in 43 of the patients. The initial leucocyte count varied greatly from a marked leucopenia to a gross leucocytosis, and, with two exceptions, the platelet count was below 150,000 per c.mm. Lymphoblasts predominated in 32 cases and myeloblasts in 11, but in 6 cases the cell type was "quite uncertain". There was one case of monocytic leukaemia in the series.

Of the 50 patients 10 were not treated and, excluding one patient who survived for 2 months, the mean survival time in this group was 12 days. Nearly all the remaining patients were initially given steroid therapy—cortisone, 150 to 200 mg. daily or prednisone 40 mg. daily. Full remission followed in 24 (60% of those treated) and partial remission in a further 6. When remissions were established, steroids were "tailed off" and an antimetabolite, 6-mercaptopurine, and aminopterin or methotrexate, were given successively. With this treatment 17 children remained in remission for periods varying from 2 to 25 months. Steroids were again administered to cover changes in treatment and in the terminal illness, when "worth-while effects" were often obtained.

Intracranial complications occurred in 4 cases, which are briefly summarized. The over-all survival time of the 40 treated children was 9.1 months. Patients with lymphoblastic leukaemia survived 11 months but, with one doubtful exception, none of the patients with acute granulocytic leukaemia responded to treatment. In this series the prognosis was poorest in leucopenic patients. *A. Ackroyd*

Respiratory System

813. Long-term Tetracycline Treatment of Chronic Bronchitis

P. S. NORMAN, E. W. HOOK, R. G. PETERSDORF, L. E. CLUFF, M. P. GODFREY, and A. H. LEVY. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 833-840, March 17, 1962. 24 refs.

In this [carefully designed] study, carried out at Johns Hopkins Hospital, Baltimore, of the effects of long-term tetracycline therapy on chronic bronchitis the data were analysed statistically by methods termed "distribution-free" or non-parametric, each patient serving as his own control. The 32 patients (23 of them male) aged 33 to 77 years had chronic bronchitis, were attending the out-patient clinic, and were followed up for 6 months to 2 years. They were given, over alternating successive periods each of 3 months, either tetracycline, 500 mg. twice daily, or an indistinguishable placebo. The two organisms most commonly isolated from the patients' sputum were *Haemophilus influenzae* and *Diplococcus pneumoniae*. There was a high degree of correlation in individual patients between the reduction in the number of these organisms in the sputum and reduced frequency of acute exacerbations. General over-all clinical improvement was seen in the patients during tetracycline therapy and the number of acute exacerbations fell to about one-third; thus there were 14 exacerbations during tetracycline treatment as compared with 44 during placebo administration. During tetracycline therapy 2 patients died; from one of these an antibiotic-resistant staphylococcus was isolated.

A. I. Suchett-Kaye

814. The Clinical Picture of Primary Chronic Nonspecific Pneumonia. (Beitrag zum Krankheitsbild der primär-chronischen, unspezifischen Pneumonie)

C. ARISI and M. SCHAMAUN. *Schweizerische medizinische Wochenschrift* [Schweiz. med. Wschr.] 92, 469-475, April 21, 1962. 3 figs., 16 refs.

Primary chronic non-specific pneumonia commonly occurs as a sequel to acute pneumonia, when after 5 to 6 weeks there is no lysis of the fibrinous exudate in the alveoli. Organization of the exudate results in scarring and shrinkage of the lung. The condition is sometimes chronic from the outset, and its aetiology is obscure. Inadequate treatment with sulphonamides and antibiotics has been adduced as one factor. In this paper the authors, who believe that the condition is becoming more frequent, report on 26 cases admitted between 1951 and 1960 to the Surgical Clinic of the University of Zurich. The series included 24 men and 2 women; 19 of the patients were aged between 50 and 70 years; 6 were under 50. The disease was practically always confined to one lobe (in 12 cases the upper lobe of the right lung). The symptoms in order of frequency were cough, sputum which was rarely blood-stained, pyrexia, thoracic pain, asthenia, loss of weight, malaise, and dyspnoea. The erythrocyte sedimentation rate was raised in all except 4 patients. The leucocyte count ranged between 7,500 and 10,000 per c.mm. Bacteriological examination of the sputum in all cases revealed a mixed infection of staphylococci, streptococci, pneumococci, and Gram-negative micro-

cocci; *Mycobacterium tuberculosis* was not found. At bronchoscopy there were signs of chronic bronchitis in 24 patients. The bronchi were mildly stenosed in 10 and compressed from without in 5. In no case was there evidence of neoplastic change.

In pathological specimens obtained from 22 patients, the macroscopic appearance of a diseased area was that of solid, scarred lung tissue empty of air, with choked bronchioles and inflammatory thickening of the mucous membrane of the medium-sized bronchi. Histologically, carnified, xanthomatous, and chronic interstitial forms were noted existing side by side in every case. Radiographs in 14 cases showed atelectatic shadows in one lobe or in one lung segment; in 8 cases there were dense hilar shadows ("hilus tumours") without atelectasis, and in 4 dense, homogeneous, irregular shadows at the periphery.

The authors draw attention to the difficulty in the differential diagnosis of primary chronic pneumonia from bronchial carcinoma. All 26 of their cases were in fact admitted to hospital on suspicion of cancer. In 4 cases only could neoplasm be excluded with reasonable certainty, and all these patients improved greatly after intensive antibiotic therapy. Operation was performed in 22 cases and there were 2 post-operative deaths. In 21 cases the result of extirpation of a single lung segment or of one lobe was excellent and lasting. Surgical treatment is indicated in every case diagnosed as of primary chronic non-specific pneumonia if (1) there is any suspicion of bronchial carcinoma, (2) suppuration associated with severe cachexia is present, or (3) there is failure to improve after 6 to 8 weeks of adequate conservative treatment.

E. S. Wyder

815. Clinical Experiences with Chemotherapy for Carcinoma of the Lung

F. L. MENDEZ JR., E. R. MAURER, H. FRECKMAN, and H. FRY. *Diseases of the Chest* [Dis. Chest] 41, 281-286, March, 1962. 3 figs., 5 refs.

The authors first review their experience of two main groups of drugs in the treatment of solid tumours, the groups being (1) alkylating agents, such as nitrogen mustard, thiotepe, chlorambucil ("leukeran"), and cyclophosphamide ("endoxan" or "cytoxan"), and (2) antimetabolites, such as methotrexate and 5-fluorouracil. In nearly all their cases the method of administration was by mouth or intravenous injection, chlorambucil, cyclophosphamide, methotrexate, and 5-fluorouracil being given orally and chlorambucil both orally and intravenously. Intra-arterial administration was attempted by cannulation of the afferent artery to the tumour during open chest surgery and also by catheterization of the pulmonary artery as at routine right heart catheterization. This technique was unsuccessful because of the chemical pneumonitis which occurred. When employed in conjunction with surgical removal of the tumour there was a high incidence of necrosis and haemorrhage. Intra-arterial perfusion was retained for treatment of tumours of the head and neck, but otherwise was abandoned.

The authors then report the results of chemotherapy in 72 cases of primary and 4 of metastatic tumour of the lung.

Of the 72 patients with primary growths, the majority of whom received chlorambucil and cyclophosphamide, there was a satisfactory response in 26 in terms of measurable reduction in the size of the tumour within 3 months, symptomatic improvement, general improvement in physical status with ability to return to work, or a gain in weight. All 4 patients with metastatic carcinoma of the breast involving the lungs showed improvement on these criteria. A case of malignant thymoma was treated successfully with 5-fluorouracil combined with x-irradiation. Nitrogen mustard was used to obtain a rapid response in a patient with superior mediastinal obstruction.

The authors state that in cases of primary lung carcinoma chlorambucil by mouth or intravenously or cyclophosphamide intravenously gave uniformly the best results. It is suggested that when the tumour is very large a course of chemotherapy before surgery renders the operation no more difficult to perform technically and may make the patient better able to withstand it. The value of chemotherapy postoperatively was demonstrated by the freedom from recurrence in 2 patients with undifferentiated small-cell carcinoma of the bronchus seen 2 years and one year respectively after surgery. The authors emphasize that care must be taken to modify the course of chemotherapy after operation, otherwise healing of the bronchial stump or wound may be delayed.

It is concluded that while surgical removal of the primary carcinoma together with drainage of lymph nodes remains the treatment of choice, chemotherapy may be of value either before or after operation in the management of inoperable carcinoma of the bronchus. *J. S. Malpas*

816. Panlobular Emphysema: Anatomy and Pathodynamics
J. P. WYATT, V. W. FISCHER, and H. C. SWEET. *Diseases of the Chest [Dis. Chest]* 41, 239-259, March, 1962. 23 figs., 48 refs.

The authors, at the University School of Medicine, St. Louis, Missouri, analysed the disturbances in ventilation, gas distribution, and intrapulmonary vascular dynamics, and the progressive structural alterations which occur in panlobular emphysema, basing their study on 275 pairs of emphysematous lungs selected at necropsy. Among these were 102 examples of panlobular emphysema, including 20 cases in emphysematous individuals who had undergone lung function tests shortly before death. The techniques used included whole-lung paper section, intravascular latex injection, the making of corrosion vinylite vascular casts, bronchoangiography, stereoscopy, and analysis of heart weight. In addition the degree of pulmonary resistance was determined by a plethysmographic technique on lungs removed shortly after death. By means of post-mortem transfusion of blood labelled with radioactive iron (^{59}Fe) a survey of the vascular bed was obtained. Autoradiographs and scintillation counts were made of whole-lung paper sections and compared with those of normal lungs.

The paramount anatomical feature of panlobular emphysema as shown by whole-lung paper sections was an even overdistension and early dissolution of the air sacs. Advancement of the disease entailed a marked deficiency of alveolar tissue. The emphysema was much more advanced in the lower lobes of the lungs, and carbonaceous pigment was diffusely scattered over the air-sac walls throughout the affected lung. Corrosion casts offered a panoramic view of

the vasculature. A basic feature of this was a generalized denudation of the arterial and arteriolar channels throughout the lung field.

Three-dimensional viewing of the latex-injected vessels showed the conversion of the normal capillary mesh into a flow pathway of coarse parallel channels. The end-result was a direct communication by 60μ channels between lobular arteries and paralobular veins.

The weight of the right ventricle was determined in 60 of the cases; this revealed that in the advanced stages of emphysema there was "a great numerical increase in hearts with right ventricular hypertrophy".

The role of airway obstruction in producing emphysema in such conditions as kyphotic chest deformities, hilar sclerosis, and neoplasia is discussed. Less well defined is the airway obstruction in chronic bronchitis and bronchiectasis observed in many cases of established emphysema; impaired clearance of entrapped pollutants may well initiate erosion of air-sac membranes. *G. Clayton*

817. The Carbonic Anhydrase Inhibitor Dichlorphenamide in Chronic Pulmonary Emphysema

P. J. CHRISTENSEN. *Lancet [Lancet]* 1, 881-885, April 28, 1962. 1 fig., 20 refs.

At the Municipal Hospital, Aarhus, Denmark, "daranide" (dichlorphenamide) was given to 9 patients with fairly severe pulmonary emphysema. The drug was begun when no further improvement was to be expected from standard therapy. During treatment with dichlorphenamide, 3 of the 9 patients felt better and were able to move about more freely without dyspnoea; one no longer had nocturnal orthopnoea. The side-effects, which were minimal, included temporary gastric discomfort, belching, slight dizziness, and transient paraesthesiae. The general effect of dichlorphenamide on the respiration was to make it deeper and slower. There was no change in minute volume, but the alveolar ventilation increased by an average of 14%, with a consequent reduction in pCO_2 . The total arterial CO_2 content fell considerably in every case, and in all but one the pH also fell. In most cases the arterial oxygen saturation improved; this was more striking when saturation before treatment was less than 80% than when it approached normal. The plasma potassium concentration tended to decrease slightly, but the plasma sodium and chloride values and the erythrocyte and leucocyte counts remained normal. The renal function was studied in 5 cases. In 3 the urinary output increased throughout the period of the study; in 4 there was a considerable rise in the output of sodium and potassium. The "CO₂ output" rose very considerably during the first day of treatment and thereafter was sustained at a more moderate level. The urinary pH rose correspondingly.

The author suggests that the mechanism of action of dichlorphenamide may be block of reabsorption of bicarbonate from the renal tubules, associated with natriuresis, osmotic diuresis, and fall in extracellular pH. The low pH would then provide a respiratory stimulus distinct from that due to CO_2 retention. *A. Gordon Beckett*

818. Subclinical Pulmonary Emphysema. Incidence and Anatomic Patterns

G. L. SNIDER, J. S. BRODY, and LER. DOCTOR. *American Review of Respiratory Diseases [Amer. Rev. resp. Dis.]* 85, 666-683, May, 1962. 14 figs., bibliography.

Urogenital System

819. **Fatal Gastric or Duodenal Haemorrhage Complicating Genito-urinary Disease.** (Tödliche Magendarmblutung als Komplikation bei urologischen Patienten) J. FRICK and H. MARBERGER. *Wiener klinische Wochenschrift* [Wien. klin. Wschr.] 74, 251-254, April 6, 1962. 30 refs.

During the 4-year period preceding this report, 3,236 patients suffering from genito-urinary disease were admitted to the Surgical Clinic of the University of Innsbruck. Of these, 1,576 had major operations on the genito-urinary tract. The total number of deaths was 90—48 among the patients who had undergone surgery and 42 among those who had no operation. The cause of death in 6 of the cases (5 of which had been treated surgically) was bleeding from a gastric or duodenal ulcer, and these 6 cases are described in detail. The authors believe that psychological stress played an important part in the aetiology of the haemorrhage. They consider that stress is an inevitable accompaniment of being in hospital and recall that in many patients there is an increased excretion of 17-ketosteroids in the urine during the first few days after admission. They suggest that patients, especially elderly ones, undergoing treatment for genito-urinary disease should be cared for under the most tranquil conditions and in addition receive tranquilizers prophylactically.

G. W. Csonka

820. **Kidney Function Studies with ¹³¹I-tagged Sodium ortho-Iodohippurate.** [Monograph, in English] G. MAGNUSSON. *Acta medica Scandinavica* [Acta med. scand.] 171; Suppl. 378, 1-124, 1962. 30 figs., bibliography.

821. **Anaemia in Renal Insufficiency.** (Anämie bei Niereninsuffizienz)

H. E. BOCK, H. NIETH, and K. SOLTH. *Deutsche medizinische Wochenschrift* [Dtsch. med. Wschr.] 87, 573-581, March 23, 1962. 4 figs., bibliography.

At the University Medical Clinic, Marburg, the serum concentrations of creatinine, urea, uric acid, phenol, non-protein nitrogen, total protein, albumin, globulins, phosphate, bicarbonate, and iron, as well as the iron-binding capacity, were determined in relation to the haemoglobin concentration and erythrocyte count in 207 patients with renal insufficiency due to chronic glomerulonephritis in 150 cases and to chronic pyelonephritis in 57. Only the serum creatinine level correlated well with the haemoglobin value and erythrocyte count. In general, the creatinine concentration rose as the haemoglobin value and erythrocyte count fell. There was also a marked negative correlation between the serum creatinine level and the circulating erythrocyte volume. The authors state that a serum creatinine level of 1.5 mg. per 100 ml. indicates a loss of one-quarter of the circulating erythrocytes, and one of 12 mg. per 100 ml. indicates a loss of one-half of these cells. Erythrocytes in the bone marrow were mostly increased in number in these patients, but the increase was poorly correlated with the serum level of creatinine and other retention substances.

M. Lubran

822. **Sodium and Potassium Excretion in Acute Renal Failure.** (Über die Natrium- und Kaliumausscheidung beim akuten Nierenversagen)

F. SCHELER and P. H. WAGNER. *Deutsches Archiv für klinische Medizin* [Dtsch. Arch. klin. Med.] 208, 159-170, 1962. 6 figs., 15 refs.

The concentrations of sodium and of potassium in the urine were investigated, at the Medical Clinic of the University of Göttingen, in 20 patients with acute renal failure, which in most of them had followed operation or abortion. The patients were treated by extracorporeal dialysis and 24-hour specimens of urine were collected at intervals during the oliguric and polyuric phases. The average sodium concentration as tested by flame photometry was 50 to 60 mEq. per litre. Only exceptionally were levels lower than 30 mEq. per litre found during oliguria. Values persistently under 30 mEq. per litre during oliguria are a strong indication that the condition is not due to significant tubular damage, but may be due to dehydration. The exclusion of acute, subacute, or chronic glomerulonephritis may be difficult. Serial estimation of sodium concentration in the urine was found to be of prognostic value, persistently high concentrations being associated with severe tubular damage or chronic renal disease. The potassium concentration in the urine of these patients averaged 30 mEq. per litre during oliguria and 20 mEq. per litre during polyuria; it lacked the diagnostic significance of the sodium concentration.

G. W. Csonka

823. **The Residual Condition and Defective Healing after Nephritis.** (Restzustände und Defektheilungen nach Nierenentzündungen)

H. SARRE. *Deutsche medizinische Wochenschrift* [Dtsch. med. Wschr.] 87, 833-838, April 27, 1962. 8 figs., 13 refs.

In a review of patients with various types of nephritis seen at the University Medical Clinic, Freiburg im Breisgau, the residual condition was assessed by clearance tests and renal biopsy examination. It was found that after acute glomerulonephritis glomerular filtration was depressed for several months, while the clearance of inulin and *p*-aminohippuric acid (PAH) was normal. In chronic nephritis there was commonly a long period of compensated renal function, and in this series half the patients were alive 10 years after the diagnosis of chronic nephritis and 12% were alive after 25 years. In some cases the findings suggested healing with residual defect. The characteristic picture showed normal clearance values and lowered glomerular filtration and no evidence of active nephritis in the renal biopsy specimen. After pyelonephritis the common picture was a raised glomerular filtration rate and lowered inulin and PAH clearance, with or without hypertension. In the group of patients with acute renal failure (associated with shock, haemorrhage, or crush injuries) the prognosis for complete renal restitution was good, provided they survived the acute phase. It is suggested that tests of inulin and PAH clearance are of great value in the diagnosis and prognosis of the renal conditions described.

G. W. Csonka

Endocrinology

824. Metopirone in the Assessment of Pituitary-Adrenal Function

A. C. BROWNIE and J. G. SPRUNT. *Lancet* [*Lancet*] 1, 773-778, April 14, 1962. 5 figs., 14 refs.

"Metopirone" (SU 4885; 2-methyl-1:2-bis(3-pyridyl)-propanone) is an amphenone-like compound which in healthy subjects inhibits adrenal 11 β -hydroxylase. This causes a fall in cortisol synthesis and thus blood concentration, so that when the pituitary-adrenal axis is intact an increased secretion of corticotrophin occurs; this in turn stimulates the adrenal cortices to produce 11-deoxycortisol (17-hydroxycorticosteroid), which can be measured in the urine. As a method of assaying pituitary corticotrophin reserve the metopirone test is indirect, since it depends on a functioning adrenal cortex.

In the test as described in this paper from Queen's College and Maryfield Hospital, Dundee, 750 mg. of metopirone was given 6-hourly for 2 days and the 24-hour excretion of urine was collected for 6 days, beginning 2 days before the drug was given. In a corticotrophin test of adrenal function 20 units of "corticotrophin-Zn" was given 6-hourly for 2 days and again 24-hour specimens of urine were collected for 6 days starting 2 days before the injection of corticotrophin. Urine was analysed for 17-hydroxycorticosteroids, 17-oxosteroids, tetrahydrocortisol, and tetrahydrocortisone. After the response in 22 healthy subjects (11 male and 11 female) aged 20 to 30 years had been evaluated 13 thyrotoxic patients (10 female and 3 male) were studied. These fell into three groups: (1) no response to metopirone but a good response to corticotrophin, 3 patients; (2) no response to either, one patient; and (3) some response to both, 9 patients, but only 3 had a rise in 17-hydroxycorticosteroid excretion within the normal range. In all 4 cases of hypothyroidism there was poor and delayed response to metopirone and the adrenal glands showed a poor response to corticotrophin.

On the basis of one case studied after long-term steroid therapy it is suggested that the poor response to metopirone is due to failure of the adrenal cortex to respond to corticotrophin rather than to failure of the anterior pituitary to secrete corticotrophin.

B. M. Ansell

825. Cardiovascular Manifestations of Acromegaly. (Manifestations cardio-vasculaires de l'acromégalie)

H. BRICAIRE, P. CHICÉ, J. ACAR, and P. BALEDENT. *Presse médicale* [*Presse méd.*] 70, 521-523, March 3, 1962. 11 refs.

According to most authorities cardiac disorders occur in approximately one-third of all patients with acromegaly. In the series of 20 cases reported in this paper from the Hôpital Broussais-La Charité, Paris, cardiovascular lesions were present in 7, in 3 of which there was unexplained cardiac failure. In all 3 cases a large heart was demonstrated radiologically, while the electrocardiogram showed left bundle-branch block in 2 of them; one of these patients died of heart failure. Of the other 4 patients in this group, 2 had hypertension with an arterial blood pressure of over 170/100 mm. Hg and 2 had coronary insufficiency; one of these suffered from angina of effort and the other sustained a

cardiac infarction. In the 13 cases in which there was no cardiovascular trouble the heart was not enlarged.

The authors consider that it is possible, as has been previously suggested, that the cardiac enlargement in at least some cases of acromegaly is part of the generalized visceral enlargement which is known to occur in this disorder. The incidence of cardiovascular complications seems higher than can be explained by chance; and such a complication is an important factor which must be taken into account when deciding the form of treatment of the endocrine lesion in each individual case—for example, the advisability or not of removing a pituitary adenoma—for it may well alter the ultimate prognosis.

G. S. Crockett

THYROID GLAND

826. Renal Function in Hyperthyroidism. (Contributo allo studio della funzionalità renale negli ipertiroidici)

R. LALLONI and P. GIACOMASSO. *Minerva medica* [*Minerva med.*] 53, 1002-1010, April 4, 1962.

This study of renal function in hyperthyroidism was made at the Ospedale Maggiore di S. Giovanni Battista, Turin. In 9 patients suffering from hyperthyroidism, some 16 aspects of kidney function were studied, including the speed of glomerular filtration (in ml. per minute), the renal blood flow (in ml. per minute), the maximum tubular excretion of the sodium salt of *para*-aminohippuric acid (in mg. per minute), and the ratio of the speed of glomerular filtration to the maximum tubular excretion. The ages of the patients (5 male and 4 female) ranged from 34 to 63 years. The basal metabolic rates (B.M.R.) before treatment ranged from +24% to +61%. In 6 of the patients the clearance studies were carried out before and after treatment with methyl-mercaptoimidazole; in 5 of these the B.M.R. had returned to normal after administration of this drug.

The authors found that their cases, considered from the standpoint of the haemodynamic function of the kidneys, could be divided into four groups. The clearance values obtained enable a working hypothesis of the vascular condition of the kidneys in hyperthyroidism to be formed. In general, the authors found that the hyperthyroid kidney reflects in its blood circulation the haemodynamic conditions prevailing in the patient, namely, increase in the minute volume and in the circulation speed determined by the tachycardia (without appreciable modification of the systolic ejection) and by the diminished peripheral resistance due to arteriolar dilatation. If endocrine factors did not intervene, the haemodynamic conditions in the kidneys of hyperthyroid patients would often lead to polyuria. The renal clearance results permit speculation as to whether: (1) only the afferent arteriole to the glomeruli is dilated, the efferent one remaining unchanged or undergoing mild constriction, or (2) both afferent and efferent arterioles are dilated, or (3) arteriolar dilatation affects only those nephrons which remained inactive in the normal kidney. That there is a close relationship between haemodynamic and functional

renal changes on the one hand and raised B.M.R. on the other is shown by the fact that when the latter returned to normal the former did likewise.

The literature is critically discussed. *V. C. Medvei*

827. A Probable Abnormality in Intrathyroidal Iodine Metabolism in Hyperthyroidism

D. W. SLINGERLAND and B. A. BURROWS. *Journal of Clinical Endocrinology and Metabolism* [J. clin. Endocr.] 22, 368-376, April, 1962. 5 figs., 20 refs.

There is evidence that some of the iodine derived from the intrathyroidal de-iodination of mono- and di-iodothyronine may be liberated from the gland, and that in healthy subjects the amount of iodine so liberated may be increased if thyroxine synthesis is blocked by antithyroid agents. From other observations, however, it seems possible that in hyperthyroidism this expected increase in the iodine liberated after antithyroid treatment may not take place.

In this paper from the Veterans Administration, Robert Dawson Evans Memorial, and Massachusetts Memorial Hospitals, Boston, a study is reported of the response to methimazole in 10 euthyroid non-goitrous subjects and 14 hyperthyroid patients following preliminary administration of radioactive iodine (^{131}I). After the antithyroid drug had been given the urinary excretion of ^{131}I in the euthyroid subjects was greater than could be explained solely on the basis of a block of thyroidal uptake of the isotope, indicating that ^{131}I had been liberated from within the gland (or from some other site of iodine-binding). Other studies, carried out simultaneously, of the pattern of disposal of ^{131}I confirmed this finding. In the hyperthyroid patients, on the other hand, the changes in ^{131}I distribution could be fully explained on the assumption that there had been an inhibition of the further uptake of ^{131}I by the thyroid gland but no significant liberation of the intrathyroidal store of ^{131}I .

The authors suggest that the difference between euthyroid and hyperthyroid states is seen because, in the latter, iodine or iodine-containing substances other than thyroxine are continuously being freed from the gland. There is thus little non-hormonal iodine available in the thyrotoxic gland. Other investigations bearing on this problem which are reported showed that iodide in large doses failed to produce any increase in the urinary excretion of ^{131}I in hyperthyroid subjects receiving methimazole, confirming the completeness of the blocking action of this drug upon the thyroidal uptake of iodine. Although they were not conclusive, further experiments failed to show any influence of methimazole upon the peripheral metabolism of thyroxine.

H.-J. B. Galbraith

828. Influence of Thyroid Hormone on Estrogen Metabolism in Man

J. FISHMAN, L. HELLMAN, B. ZUMOFF, and T. F. GALLAGHER. *Journal of Clinical Endocrinology and Metabolism* [J. clin. Endocr.] 22, 389-392, April, 1962. 4 refs.

The concentration of thyroid hormone influences the degradation pathways of steroid hormones such as testosterone, dehydroisoandrosterone, and hydrocortisone. An investigation was carried out at the Sloan-Kettering Institute for Cancer Research, New York, designed to determine whether the metabolism of oestradiol, a hormone chemically dissimilar to these steroids, was also influenced by the thyroid state. Five schizophrenic patients and 2 healthy subjects

were studied before and after they had received triiodothyronine (200 μg . daily for 8 to 28 days) and 2 hyperthyroid patients and 2 patients with myxoedema were similarly studied before and after they had been rendered euthyroid by treatment. Oestradiol labelled with radioactive carbon was administered to each subject and its urinary excretion products were examined by extraction, fractionation, and measurement of the radioactivity in each fraction.

The proportion of the dose of radioactivity recovered in the urine and the percentage of the total steroid excretion which was present in the form of glucuronate was unaffected by the change induced in the thyroid state. However, when the thyroid state was at the higher level, the proportion of the hormonal metabolites present in the oestrial fraction decreased by 35 to 68%. At the same time, the excretion of 2-methoxyoestrone was increased and the oestrone conversion was also altered, although this change was less consistent. That thyroid hormone influences the pattern of oestradiol metabolism is therefore confirmed. It is also pointed out that the results of these studies reveal evidence that oestrogen metabolism in schizophrenic patients differs from the normal.

H.-J. B. Galbraith

829. Studies on the Cytotoxic Factor in Thyroid Disease

W. J. IRVINE. *British Medical Journal* [Brit. med. J.] 1, 1444-1449, May 26, 1962. 11 figs., 17 refs.

The nature of the cytotoxic factor present in the serum of certain patients with thyroid disease has been studied at the University of Edinburgh by observation of its effect upon trypsinized human thyroid cells in tissue culture. In the main, thyroid cells from patients with thyrotoxicosis were the most susceptible, while those from patients with simple goitre were relatively unaffected. Fractionation of serum containing the cytotoxic factor by column chromatography and electrophoresis showed the factor to be associated with the γ -globulin fraction, and immunological studies showed a parallelism between the complement-fixing antibody and cytotoxic factor and a lack of correlation between this activity and thyroglobulin antibodies. Subcellular fractionation of tissue from a thyrotoxic goitre showed the complement-fixing antigen and the antigen corresponding to the cytotoxic factor to be located in the same fractions and further supported the probable identity of the cytotoxic and complement-fixing autoimmune systems. The rapidity of the cytotoxic effect *in vitro* is contrasted with the slow development of Hashimoto's disease, where the factor occurs in high levels in the serum. Non-trypsinized cells from human thyroid were not affected by serum containing the factor.

F. W. Chattaway

830. Deficiency of Vitamin B₁₂ in Hypothyroidism

G. R. TUDHOPE and G. M. WILSON. *Lancet* [Lancet] 1, 703-706, April 7, 1962. 2 figs., 25 refs.

At the Royal Infirmary, Sheffield, 52 patients suffering from spontaneous primary hypothyroidism were studied during maximum histamine stimulation in order to assess the amount of gastric acid secretion. This showed that achlorhydria was present in 24 patients, of whom 6 had been receiving thyroxine for periods ranging from one to 5 years. Pernicious anaemia, diagnosed on the basis of the blood picture, achlorhydria, a low serum level and impaired absorption of vitamin B₁₂, and response to therapy with the vitamin, was found in 9 patients. Serum vitamin B₁₂ con-

centration was also low in most of the 15 patients with achlorhydria but without pernicious anaemia, being over 200 μg . per ml. in only 2 of these patients, whereas it was under 200 μg . per ml. in only one of the patients without achlorhydria. Absorption of vitamin B₁₂ as measured by its urinary excretion was below 5% in 24 hours in all the patients with pernicious anaemia and was below 10% in 7 of the 11 achlorhydric patients so tested; the urinary excretion rate was low in those with a low serum vitamin B₁₂ level. Gastric biopsy examination showed atrophy of the mucosa in those patients with a low vitamin B₁₂ concentration, but a normal mucosa in the others.

It is suggested that in these patients there may be a common aetiological factor tending to destroy both the gastric mucosa and the thyroid gland. *E. H. Johnson*

DIABETES MELLITUS

831. Acetohexamide: Preliminary Report on a New Oral Hypoglycaemic Agent

G. E. MAHA, W. R. KIRTLEY, M. A. ROOT, and R. C. ANDERSON. *Diabetes [Diabetes]* 11, 83-90, March-April, 1962. 8 figs., 19 refs.

This paper reports preliminary clinical and animal trials of acetohexamide, an oral hypoglycaemic agent synthesized in the Lilly Research Laboratories. Acetohexamide is a sulphonylurea compound with greater hypoglycaemic potency than tolbutamide in animals and man. It did not produce any serious toxic effects in mice, rats, dogs, or man, and no indication was found that its mechanism of action differed in any way from that of other sulphonylurea compounds.

More than 150 diabetic patients were treated with acetohexamide at Marion County General Hospital, Indianapolis, Indiana. Of these, 43 had been under treatment for 12 to 19 months and "good" or "fair" control was achieved in about half of them. The patients were mainly elderly and obese. Of 20 patients who showed a "good" or "fair" response, control was achieved with 250 or 500 mg. of acetohexamide per day in 17. Increasing the dose above 1,000 mg. per day did not increase the incidence of satisfactory response. *K. O. Black*

832. The Use of Oral Hypoglycaemic Agents

E. TOLSTOI, M. G. GOLDNER, I. S. KLEINER, W. S. NORTON II, and J. POMERANZE. *Bulletin of the New York Academy of Medicine [Bull. N.Y. Acad. Med.]* 38, 323-347, May, 1962. 5 figs.

833. Outpatient Assessment of Oral Hypoglycaemic Drugs
J. P. BINGLE, F. E. HIGGINS, and R. E. TUNBRIDGE. *Lancet [Lancet]* 1, 717-720, April 7, 1962. 18 refs.

At the General Infirmary at Leeds the hypoglycaemic action of a new oral sulphonylurea, BH 135, was compared with that of chlorpropamide in 40 elderly out-patients with mild diabetes. The dosages compared were 200 and 400 mg. daily of BH 135, and 250 and 500 mg. daily of chlorpropamide, the patients receiving each drug in turn for 8 consecutive weeks. The lower dosage of both drugs was compared in 14 patients, and the higher dosage in the remaining 26 patients. Assessment was made symptomatically (loss of weight, ketosis, polydipsia, polyuria) from the blood

sugar level estimated 24 hours after breakfast and the sugar content of the urine recorded by the patient with "clintest", several scoring methods being used to express sugar concentration. The assessments were made fortnightly throughout the 16 weeks of the trial.

Of the 40 patients 3 had to be given insulin following poor control with both hypoglycaemic drugs; in addition, in 2 patients treatment had to be changed from BH 135 to chlorpropamide because of lack of diabetic control. The mean blood sugar level over the whole period of the trial was significantly lower with chlorpropamide therapy than with BH 135. Further analysis showed that this difference was evident only with the larger doses of both drugs, and applied also if the blood sugar level was compared at each fortnightly period. The clintest scoring for 2%, 1%, 0.5%, and 0% respectively of the sugar content of the urine was variously 4, 3, 2, 1; 4, 2, 1, 0; and 2, 2, 0, 0. Whatever the method there was still a significant decrease in the mean score over the 8-week period of 500 mg. of chlorpropamide compared with 400 mg. of BH 135, but not with the lower doses.

The authors suggest that the form of the present trial does not inconvenience the patients unduly and is sufficiently reliable as a pilot assessment in the comparison of a new hypoglycaemic drug with one of established value. Finally, they conclude that BH 135 is certainly no better than, and may be inferior to, chlorpropamide. *Gerald Sandler*

834. Long-term Experience with Chlorpropamide in Diabetes Mellitus

D. R. HADDEN, D. A. D. MONTGOMERY, and J. A. WEAVER. *Diabetes [Diabetes]* 11, 91-95, March-April, 1962. 1 fig., 15 refs.

Records are available of 353 diabetic patients treated with chlorpropamide since 1958 at the Royal Victoria Hospital Belfast, and the authors report their findings with regard to clinical response and toxic effects in this group over 2 years. The patients who responded to treatment were over 40 years of age, and it was clear that chlorpropamide did not widen the spectrum of diabetic patients who will respond to sulphonylurea compounds. Nevertheless it was most potent in lowering the blood sugar level, with the result that more satisfactory control was achieved in some patients than with tolbutamide. The toxic effects of chlorpropamide were minimal. Jaundice developed in 3 patients, but in only one of them does it seem to have been due to chlorpropamide. *K. O. Black*

835. Comparative Pharmacology of the Sulphonylureas

R. S. RADDING, L. R. KERN, and J. C. OWENS. *Metabolism. Clinical and Experimental [Metabolism]* 11, 411-415, April 1962. 3 figs., 4 refs.

A study of the comparative efficacy of acetohexamide, thiohexamide, chlorpropamide, and tolbutamide is reported from Hermann Hospital, Houston, Texas. It was found that tolbutamide in all dosages had the least hypoglycaemic action and that 1,000 mg. had no greater effect than 500 mg. The authors concluded that at the dosage level of 250 mg. chlorpropamide exerted a significantly greater effect than any of the other drugs. However, final conclusions about the hypoglycaemic efficacy of these sulphonylureas must await investigation of the duration of their activity. *I. McLean Baird*

The Rheumatic Diseases

836. **Medullary Iron in Rheumatic Diseases.** (Le fer médullaire dans les maladies rhumatismales) C. MOURIQUAND, E. LEJEUNE, D. GERMAIN, and J. MAÎTRE-PIERRE. *Nouvelle revue française d'hématologie* [Nouv. Rev. franç. Hémat.] 2, 55-69, Jan.-Feb. [received April], 1962. 2 figs., bibliography.

From the Institut Pasteur, Lyons, comes this report of an investigation into the marrow iron stores in 108 children and 59 adults with rheumatic diseases. None of these patients had a blood disease accompanying the rheumatic process. In the bone-marrow examination smears were stained with Prussian blue in order to determine the percentage of "sideroblasts", since these serve as a measure of the "extra-erythroblastic" marrow iron.

It was found that during the active phases of rheumatic diseases the amount of extra-erythroblastic iron increases, while the intra-erythroblastic iron decreases or disappears. This process returns to normal when the inflammatory process abates. The significance of these findings is discussed and it is noted that the decrease of "intra-erythroblastic" iron is characteristic of active inflammatory disease.

I. McLean Baird

ACUTE RHEUMATISM

837. **Rheumatic Fever Treated with Penicillin in Bactericidal Dosage for Six Weeks: Report of a Small Controlled Trial**

M. E. CARTER, E. G. L. BYWATERS, and G. T. G. THOMAS. *British Medical Journal* [Brit. med. J.] 1, 965-967, April 7, 1962. 3 refs.

During 1959 and 1960 an investigation was carried out at the Rheumatism Research Unit, Taplow, Bucks, to determine whether bactericidal doses of penicillin given for 6 weeks had any influence on the cardiac state of patients who had had a recent attack of rheumatic fever. Of the 51 patients included in the trial, none of whom had had hormone therapy, 26 were given large therapeutic doses of penicillin (test group) and 25 were given prophylactic doses only of penicillin by mouth (control group). Both groups received moderate doses of salicylates in addition; hormone treatment was not given. The cardiac status of the patients was determined at the beginning of treatment and again one year later. Carditis was present at the onset in 19 patients in each group; in the remainder abnormal cardiac signs did not develop until later, irrespective of the group to which the patients belonged. Most of the patients with carditis had improved at the end of one year, and although those in the test group fared rather better than the controls, the difference between the two was not significant. The mean interval before antistreptolysin-O titre reached normal levels was 23.7 weeks in the test group and 17.9 weeks in the controls.

The authors state that these results do not confirm the findings of Mortimer *et al.* (*New Engl. J. Med.*, 1959, 260, 101) that treatment with bactericidal doses of penicillin is valuable in rheumatic fever.

[The incidence of "carditis" in the present series is high, but as Grade-1 or Grade-2 systolic murmurs were taken as evidence of carditis, this is to be expected. Many physicians would not regard such murmurs as of organic origin.]

John Lorber

838. **Evaluation of the Streptococcal Desoxyribonuclease B and Diphosphopyridine Nucleotidase Antibody Tests in Acute Rheumatic Fever and Acute Glomerulonephritis**

E. M. AYOUB and L. W. WANNAMAKER. *Pediatrics* [Pediatrics] 29, 527-538, April, 1962. 6 figs., 24 refs.

The extracellular products of Group-A streptococci are often antigenic and measurement of the antibody response to streptolysin O, hyaluronidase, and streptokinase has been of practical help in the diagnosis of infection.

In this paper from the University of Minnesota, Minneapolis, the authors describe the serological response in controls and patients with acute rheumatic fever and glomerulonephritis to two newly discovered streptococcal enzymes, diphosphopyridine nucleotidase (DPNase) and deoxyribonuclease B (designated DNase B), the most useful of four such enzymes. Titres were determined on the first available blood sample from 60 patients with acute rheumatic fever and 46 with glomerulonephritis, and compared with the titres in serum from 70 controls.

Whereas in 19% (by definition) of controls there was a raised antistreptolysin O (ASO) titre and in the same percentage there were increased titres for anti-DPNase and anti-DNase B, 82 to 83% of patients with rheumatic fever had raised titres. Of patients with glomerulonephritis, 96% had raised titres of ASO, 76% of anti-DNase B, and 91% of anti-DPNase. In each age group the anti-DPNase titres tended to be higher in patients with acute nephritis than in those with acute rheumatic fever. While samples were taken from patients with nephritis on the average one week earlier than from rheumatic fever patients (in relation to the onset of previous upper respiratory-tract infection) this did not seem to account for the observed differences. The findings are in accord with those of a previous report which showed that nephritogenic strains of streptococci have a high frequency of DPNase production *in vitro* compared with other Group-A strains. The authors conclude that these two new antibody tests are particularly useful in providing evidence of preceding streptococcal infection in patients who fail to show a raised ASO titre.

E. G. L. Bywaters

839. **Disadvantageous Circulatory Effects of Salicylate in Rheumatic Fever**

W. D. ALEXANDER and G. SMITH. *Lancet* [Lancet] 1, 768-771, April 14, 1962. 1 fig., 22 refs.

Since some workers have reported deterioration in the cardiac status of patients given salicylates for rheumatic fever, the present authors studied 50 patients with rheumatic fever admitted to the Clinical Chemotherapeutic Research Unit of the Medical Research Council, Glasgow. The patients were given salicylate in a dosage which would maintain a serum level of 40 mg. per 100 ml. and were

carefully observed for evidence of cardiac failure. None had failure on admission, but in 9 (all aged 12 years and over) some signs of failure developed 2 to 8 days after the start of salicylate administration. Failure did not develop in any of the patients after the eighth day. The commonest signs of failure were over-filling of the neck veins and crepitations at the lung bases. The serum salicylate level in the first 8 days in the patients in whom failure developed was similar to that in patients without failure (40.1 ± 3.5 and 39.0 ± 1.4 mg. per 100 ml.), suggesting that the onset of failure was not due to the presence of an unusually high salicylate level. [These levels were, nevertheless, very high indeed and known to be on the borderline of serious toxic side-effects.] Of the 9 with failure 8 had undoubted carditis at the onset. It is considered unlikely that these patients would have developed cardiac failure just at that stage had they been treated with rest in bed only, since the duration of the illness before salicylate treatment was very variable.

Six other patients (adults) with established rheumatic valvular disease were studied during cardiac catheterization. They were given a [very large] dose of 7 g. of sodium salicylate in 70 ml. of water by mouth during this procedure. Cardiac output was measured, the Fick principle being used, before and after the dose. There was considerable increase in the metabolic rate and the increase in ventilation was directly proportional to the increase in oxygen consumption. The arterio-venous oxygen difference and the cardiac output rose significantly. The increase in cardiac output was effected almost entirely by an increase in stroke volume.

It is concluded that doses of salicylate which may cause increased cardiac output are best avoided where there is clear evidence of carditis. [It is hardly necessary to-day to give such very large doses when steroids are available.]

John Lörber

CHRONIC RHEUMATISM

840. Femoral Head Destruction in Rheumatoid Arthritis and Osteoarthritis: a Clinical Review of 27 Cases
I. C. ISDALE. *Annals of the Rheumatic Diseases* [Ann. rheum. Dis.] 21, 23-30, March, 1962. 4 figs., 12 refs.

At the Queen Elizabeth Hospital, Rotorua, New Zealand (the national hospital for rheumatic diseases), radiological examination of the hip region was performed in some 600 patients, of whom about 300 had rheumatoid arthritis. Hip absorption was found in 27 patients, 15 with rheumatoid arthritis (10 females and 5 males) and 12 with osteoarthritis (9 females and 3 males). The degree of absorption varied. Whenever possible, superimposition tracings were taken in order to demonstrate the progress of destruction, and the area of the femoral head was measured with a planimeter. In nearly every case there was evidence of protrusion acetabuli or destruction of the superior aspect of the acetabulum. Both hips were affected in 8 cases. Little correlation was established between the amount of destruction and the severity of the pain. Only 10 of the patients had received steroid drugs, and in some of them it seemed improbable that the drug treatment was related to the hip absorption. The author concludes that the risk of hip absorption is too small to warrant discontinuance of intra-articular injections of steroid drugs in rheumatoid arthritis and osteoarthritis.

A. Garland

841. Dystrophic Bone Changes in the Shoulder following Local Injections of Corticosteroids (Case Reports of Five Patients Treated for Scapulo-humeral Periarthritis). (Altérations osseuses dystrophiques de l'épaule survenues après injections locales de corticostéroïdes (Étude de cinq observations de malades traités pour périarthrite scapulo-humérale))
G. H. FALLET, J. FASEL, E. NAZ, and R. LAGIER. *A.I.R. Archives of Interamerican Rheumatology* [A.I.R. Arch. Interamer. Rheum. (Rio de J.)] 4, 543-578, Dec., 1961 [received April, 1962]. 8 figs., bibliography.

This is a study, made at the University of Geneva, of 5 patients with scapulo-humeral periarthritis who developed bone changes after local injections of corticosteroids. Staphylococcal arthritis preceded the bone changes in 3 of the patients, while in the other 2 no evidence of infection was found. The clinical course was similar in all 5. The injections had been intra-articular in 4 (including the 3 who had had staphylococcal arthritis) and para-articular in one. X-ray examination showed destruction of bone, mainly in the upper part of the head of the humerus, and generalized osteoporosis. Surgical treatment, performed under antibiotic cover, consisted in removal of diseased bone by curettage of the head of the humerus followed by packing with spongy bone. The important fact emerging from this study is that changes of the type described may be caused by the injection of cortisone and should not be confused with primary infective lesions arising within the shoulder joint.

Peter Ring

842. Corticosteroid Therapy of Rheumatoid Arthritis Supplemented with Methandrostenolone
G. M. CLARK and D. MILLS. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 156-162, April, 1962. 6 refs.

An anabolic hormone, methandienone (methandrostenolone), was found to have a steroid-sparing effect when administered with prednisone to patients with rheumatoid arthritis. To 12 patients showing signs of steroid over-dosage methandienone was given in a dosage of 15 mg. daily for 6 weeks, after which time it became possible to reduce the dosage of prednisone from 15.2 mg. to 4.2 mg. daily. At the same time there was an improvement in the arthritis, without, however, any detectable change in osteoporosis. That this improvement was not merely due to coincident supportive measures was shown by similar improvement in 12 out-patients who were given the anabolic hormone in a dosage of 10 mg. daily. One patient was proved to change from negative to positive nitrogen balance while receiving the hormone. In all the patients given methandienone "bromsulphalein" clearance was reduced, but this returned to normal when the hormone was withdrawn. No other liver function tests were affected.

[Other workers have reported reduced bromsulphalein clearance caused by anabolic hormones related to testosterone, probably due to stasis in bile canaliculi, although jaundice is rare.]

J. A. Cosh

843. Idiopathic Osteoarthritis of the Hip
J. R. PEARSON and D. M. RIDDELL. *Annals of the Rheumatic Diseases* [Ann. rheum. Dis.] 21, 31-39, March, 1962. 15 figs., 7 refs.

During a period of 15 years, 203 men and 197 women with idiopathic osteoarthritis of the hip received treatment at the Robert Jones and Agnes Hunt Orthopaedic Hospital,

■Oswestry. Most of the patients were aged over 50 years. The clinical findings were reviewed and the severity of pain was estimated by the dosage of analgesics needed to control it, the presence of pain at night, the distance the patient could walk, and the need to use one or 2 sticks. Stiffness was not a major complaint. Skiagrams were examined with special attention to sclerosis, cysts, osteophytes, and changes in the joint space. Assessment of the findings led to the conclusion that osteoarthritis of the hip occurs in one or other of 2 patterns. In the early stages, limitation of extension and of internal rotation, followed by flexion deformity and limitation of flexion, is common to both patterns. In one of the patterns there next occurs a decrease in abduction and external rotation, with loss of side-to-side movements. The superior part of the joint shows maximal loss of joint space and the greatest degree of sclerosis and cyst formation. Osteophytes form round the acetabular margin and the rim of the femoral head. Upward subluxation of the head of the femur often takes place and the neck of the bone may present a valgus deviation. In the other pattern, adduction deformity does not occur and the greatest loss of joint space and the greatest degree of sclerosis and cyst formation appear medially in the deepest part of the joint. A varus femoral neck often develops. The adduction-external rotation and the non-adducted types of hip were found in 311 and 89 cases respectively. These findings are of interest in view of the widely held belief that all osteoarthritic hips adduct.

A. Garland

COLLAGEN DISEASES

844. Isolation of Antibody-Like Gamma-globulin from Lupus Glomeruli

P. FREDMAN and A. S. MARKOWITZ. *British Medical Journal* [Brit. med. J.] 1, 1175-1178, April 28, 1962. 13 refs.

In an earlier study the authors (*Lancet*, 1959, 2, 45) demonstrated gamma-globulin and complement in the renal lesions of glomerulonephritis and systemic lupus erythematosus. In the present study at St. George's Hospital, London, and the Hektoen Institute for Medical Research, Chicago, they investigated the immunological activity of protein eluted from kidney glomeruli by citrate buffer at pH 3.2.

Material eluted from 3 kidneys at pH 7.2 contained no gamma-globulin as measured by a precipitin test. The eluate at pH 3.2 from normal kidney glomeruli contained no gamma-globulin, but that from glomeruli of single kidneys affected by glomerulonephritis and systemic lupus erythematosus contained gamma-globulin.

When the kidneys were stained by the immunofluorescent technique for bound gamma-globulin, staining of the glomerular capillary wall was seen in the glomerulonephritic and lupus kidney. The normal kidney did not stain. With immunofluorescent staining for gamma-globulin the eluate from the lupus kidney caused inconstant staining of the glomerular capillary wall and slight staining of the nuclei of liver cells. When fresh serum was added, bright staining of liver and kidney nuclei and some staining of the glomerular capillary were seen. This enhancing activity was removed by heating the serum at 60° C. and could not be duplicated in an experiment with guinea-pig serum. Since when anticomplement serum was used the eluate from the lupus kidney together with fresh human serum stained nuclei,

it seemed likely that the enhancing action of human serum was due to complement and that the factors binding to the nuclei were complement-fixing gamma-globulin antibodies.

The authors suggest that the failure to elute antibody from the kidney of a patient with glomerulonephritis may have been due to failure to discover the appropriate conditions, and that in systemic lupus erythematosus at least part of the gamma-globulin eluted from the glomeruli was identical to the circulating antinuclear factor which is almost always present in systemic lupus erythematosus.

G. L. Asherson

845. Effect of Serotonin Inhibitors on Connective Tissue Disease: Experimental and Clinical Studies

A. L. SCHERBEL and E. A. SCHEID. *Cleveland Clinic Quarterly* [Cleveland Clin. Quart.] 29, 1-15, Jan. [received April], 1962. 4 figs., 16 refs.

Previous observations have suggested that serotonin, histamine, and noradrenaline may affect the connective-tissue system and therefore that they may be implicated in the pathological manifestations of various connective-tissue disorders. The present authors used the serotonin antagonists—methysergide bimalate, cyproheptadine, and KB-95, a pyrazole derivative—in rheumatoid arthritis and primary systemic sclerosis. These preparations were given intravenously and/or orally to 162 patients with rheumatoid arthritis of at least one year's duration before treatment was started and to 15 patients with primary systemic sclerosis. In 85 selected patients with rheumatoid arthritis the use of serotonin inhibitors was continued for one year or longer.

KB-95 was the most and methysergide bimalate the least effective, and all three drugs were more effective when given intravenously than orally. Pain began to diminish 4 to 6 hours after intravenous infusion; swelling and stiffness of the joints lessened, but muscular weakness did not diminish—rather the reverse in some instances. After 7 to 10 days' treatment many patients complained of drowsiness, light-headedness, apathy, and hallucinations. A beneficial effect was observed following intra-articular injection of the drugs, lasting some 7 to 10 days with KB-95, but only 2 to 3 days with methysergide.

The response to oral therapy was not consistent; only 11 out of the 60 patients so treated responded rapidly. Administration of an amine oxidase inhibitor in addition lessened the psychogenic effects of the serotonin inhibitor without appearing to diminish the initial effects upon the joints. The serotonin inhibitors seemed to enhance the anti-inflammatory action of prednisone, and hypersteroidism occurred in some patients who were maintained on a comparatively low dose of corticosteroids for 6 months in addition to receiving amine oxidase inhibitors.

In the 15 cases of systemic sclerosis the serotonin inhibitors were again more effective when given intravenously than orally and KB-95 yielded the best results; in fact, the results with methysergide could only be considered as equivocal. The treatment led to softening of the skin and subcutaneous tissue as well as of some of the calcified deposits, and to lessening of the vasomotor reaction and the healing of ulcers.

The authors make no undue claims, but suggest that the results indicate the need to study more extensively the effect of amine oxidase inhibitors and tissue amine releases in all disease processes, particularly the connective-tissue disorders.

R. E. Tunbridge

Neurology and Neurosurgery

846. The Action of *laevo*-Glutamine on Disturbances of Consciousness in Neurosurgery. (Action de la lévoglutamine sur les troubles de la conscience en neurochirurgie) J. LE BEAU, P. PRADAT, and M. TOULMONDE. *Revue neurologique* [Rev. neurol.] 106, 25-33, Jan. [received May], 1962. 4 refs.

An account is given of the initial experiences at the Salpêtrière, Paris, of L-glutamine in the treatment of disorders of consciousness. Initially a number of patients were given small doses (up to 120 mg. in 24 hours) of this substance, which is the monoamide of L-glutamic acid. No toxic effects were observed and some benefit seemed to accrue in some of the cases. Later, a series of 43 patients were given high doses (up to 720 mg. a day). This group included patients who had recently undergone neurosurgical operations, 8 patients with cerebral tumour, and others suffering from disturbance of consciousness following head injury and from spontaneous intracranial haemorrhage. L-Glutamine appeared to exert a favourable effect in accelerating the return to a normal level of consciousness in those patients in whom spontaneous recovery could be expected. Occasionally, the drug seemed to be effective even in cases which would normally carry a bad prognosis, and the authors consider that further trial of the drug is desirable.

J. B. Stanton

847. A New Miotic Pupillary Reaction to Change of Position in Rabbits. (Über eine neue miotische Pupillenreaktion auf Änderung der Körperlage beim Kaninchen) R. OTSUKA and A. EINLEITUNG. *Archiv für Psychiatrie und Nervenkrankheiten* [Arch. Psychiat. Nervenkr.] 202, 606-615, 1962. 3 figs., 12 refs.

When a rabbit is placed on its back a marked bilateral miosis results, but when it is laid on its side miosis occurs only in the upper eye. Since this reaction persists even after section of the posterior commissure, it is therefore not due to light, and since it is not altered on stimulating the skin it is therefore different from the pupillary-skin reflex. The reaction is abolished if the animal is curarized, leading to the conclusion that the reflex arc begins in the medial rectus oculi muscle. The reflex is in fact thought to be related to the convergence-accommodation reflex in the human eye, and if this is indeed so it will thus be possible to study this phenomenon for the first time in experiments on animals.

The above-described pupillary reflex could not be elicited in other species such as the cat, dog, guinea-pig, frog, chicken, goat, or sheep. The authors speculate that the rabbit occupies a borderline position as regards monocular and binocular vision. Although its vision is mainly monocular a few uncrossed visual fibres were found, suggesting that there is a trace of binocular vision. Miosis or near vision is a function of binocular vision, and in the human subject miosis or near vision is always bilateral. In the rabbit, because of its evolutionary borderline position, the reflex can occur unilaterally.

J. Hoenig

848. Evaluation of Function of the Cerebral Hemisphere by Intracarotid Injection of "Sodium Amytal". (Évaluation par injection intra-carotidienne d'amytal sodique de la valeur fonctionnelle d'un hémisphère) B. PERTUISSET and G. ARFEL. *Revue neurologique* [Rev. neurol.] 106, 14-24, Jan. [received May], 1962. 2 figs., 15 refs.

The aim of this study, carried out at the Hôpital de la Pitié, Paris, was to assess the value of amylobarbitone sodium injection as a means of foretelling if motor loss or speech disorder would follow hemispherectomy in patients with cerebral atrophy or tumour of the basal ganglia. The procedure enables the function of the injected hemisphere to be evaluated. Intracarotid injections of a 10% solution of amylobarbitone sodium were given under local anaesthesia to 5 patients with hemiplegia who had received premedication with 50 mg. of promethazine hydrochloride intramuscularly. All 5 received injections on the side of the abnormal hemisphere; 2 also received injections on the side of the normal hemisphere. The dose of amylobarbitone sodium was 250 mg. on the side of the abnormal hemisphere and 50 mg. on the opposite side. The time taken for the injection varied from 4 to 80 seconds. An electroencephalogram (EEG) was recorded throughout the injection, and the contralateral half of the body was observed clinically. Injection of a normal hemisphere resulted in flaccid hemiplegia on the opposite side, disturbance of consciousness, and, where the hemisphere was the dominant one, dysphasia. Injection of a damaged hemisphere did not alter an existing hemiplegia or cause speech disturbance, but did produce disturbance of consciousness in 3 of the 5 cases. The disturbance of consciousness appeared later and lasted longer than when the injection was made into the normal hemisphere. In the other 2 cases a lesion of the thalamus was present, and this leads the authors to speculate whether the method may not also be used to evaluate thalamic function. In both normal and abnormal hemispheres slow waves appeared on the EEG about 16 seconds after the injection. They persisted longer in the abnormal hemisphere than in the normal one. In one case epileptic phenomena previously present in the EEG tracing were greatly accentuated on the damaged side when amylobarbitone was injected into that side; the fits disappeared after hemispherectomy. The authors recommend wider use of this harmless method for exploring the functions of the central nervous system.

G. S. Crockett

849. The Treatment of Huntington's Chorea with Trifluoperazine (Stelazine) N. H. COHEN. *Journal of Nervous and Mental Disease* [J. nerv. ment. Dis.] 134, 62-71, Jan. [received April], 1962. 3 figs., 29 refs.

In an attempt to determine the efficacy of the phenothiazines in the symptomatic treatment of Huntington's chorea the author has treated 7 patients with trifluoperazine ("stelazine"). The drug was given in a daily dose of 2 mg.

for the first 3 days, and this was gradually increased until a therapeutic dose was attained. Three points were considered in assessing improvement: diminution in chorea, increase in functional activities, and improved dexterity. All the patients showed a moderate to marked improvement (50 to 75%) in choreiform movements, and all showed a pronounced improvement (48 to 94%) in functional activity. Dexterity also improved, one patient being able to return to work after a break of 2 years. Side-effects were almost completely absent, except for mild masking of the facies in 2 cases. To determine the effects of discontinuing treatment medication was stopped in 3 cases which had much improved. After 5 days there was complete reversal of the improved condition, which returned, however, when the drug was readministered.

Of 3 patients tested with the Wechsler Adult Intelligence Scale, 2 showed continual deterioration, and in one there was no change in the deterioration scores after 6 months. The general clinical impression was that trifluoperazine did not reverse the process of intellectual deterioration.

The method of action of trifluoperazine is discussed, and it is suggested that it produces a Parkinsonian effect which counteracts the uncontrolled movements of chorea.

E. H. Johnson

850. Epilepsy and Disseminated Sclerosis

W. B. MATTHEWS. *Quarterly Journal of Medicine [Quart. J. Med.]* 31, 141-155, April, 1962. 8 figs., 34 refs.

Among 200 patients in whom disseminated sclerosis (D.S.) had been diagnosed at the Derbyshire Royal Infirmary, Derby, were 13 who were thought to be also suffering from epilepsy. In this paper the author presents "a critical analysis of the incidence and significance of epilepsy as a symptom of D.S." based on these 13 cases, 9 of which are described in detail, and of 58 cases recorded in the literature. The first of the author's patients, in whom D.S. was diagnosed on very strong clinical evidence and who developed fits 6 years after the onset of symptoms related to the central nervous system, proved to have an extensive angiomatous malformation. In Case 2, in which D.S. was well established but which was originally thought to be a case of epilepsy, the patient had tonic seizures in one arm which were not epileptic in nature. The third patient had D.S. and an astrocytoma. In Cases 4 and 5 the fits preceded the onset of D.S. for a long time and it was thought that these patients were suffering from idiopathic epilepsy as well as D.S. In 3 cases epileptic seizures occurred during exacerbations of D.S. A further patient, who had had nocturnal fits for 10 years since the age of 38, developed obvious D.S. 2 years after the fits ceased, and it is thought that the epilepsy might have been a symptom of D.S.

The author concludes that chronic epilepsy is seldom caused by D.S. and that fits occurring without obvious relevance to the course of the disease should give rise to a suspicion that demyelination may not be the cause of the fits.

H. S. Schutta

851. Disturbances of Swallowing and Esophageal Motility in Patients with Multiple Sclerosis

D. D. DALY, C. F. CODE, and H. A. ANDERSEN. *Neurology [Minneapolis]* 12, 250-256, April, 1962. 7 refs.

Of 29 patients seen at the Mayo Clinic suffering from disseminated sclerosis 16 had difficulty in swallowing, in one case this being the presenting symptom. The authors

state that no single type of disorder of swallowing is characteristic of the disease; thus difficulty in the earliest phase of swallowing was observed in 4 patients, choking not due to palatal weakness was reported by 10 patients, while 12 patients noted "sticking" of the bolus during the late phase of swallowing.

In 26 of these patients, including the 13 who had specifically denied any difficulty in swallowing, studies of oesophageal motility were undertaken, the method being fully described. In 15 patients various abnormalities were observed. Of the 13 patients showing disturbances in function of the gastro-oesophageal sphincter this consisted in poor relaxation of the sphincter in 11 cases, poor relaxation associated with excessive contraction of the sphincter in one case, and excessive contraction of the sphincter alone in one case. Poor relaxation of the pharyngo-oesophageal sphincter was noted in only one case. Disturbances of motility of the oesophagus occurred in 11 patients; in 4 deglutition was incoordinated and repetitive contraction was noted in response to the passage of a bolus, and in 5 patients swallowing induced diffuse spasm of the oesophagus. The authors conclude that the pathogenesis of abnormal oesophageal motility in disseminated sclerosis is not clear and note that similar abnormalities have been observed in other neurological disorders such as encephalitis, infarction of the brain stem, and diffuse cerebral trauma. A. G. Freeman

852. Serum Enzyme Studies in Muscular Dystrophy. III. Serum Malic Dehydrogenase, 5-Nucleotidase and Adenosine-triphosphatase

S. R. CHOWDHURY, C. M. PEARSON, W. W. FOWLER JR., and W. H. GRIFFITH. *Proceedings of the Society for Experimental Biology and Medicine [Proc. Soc. exp. Biol. (N.Y.)]* 109, 227-230, Jan. [received April], 1962. 16 refs.

It is now well known that the levels of certain enzymes in serum, normally very low or undetectable, are characteristically raised in a variety of pathological conditions. In this study reported from the University of California, serum levels of malic dehydrogenase (MDH), 5-nucleotidase, adenosine triphosphatase (ATPase), glutamic-oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT), lactic dehydrogenase (LDH), and aldolase were estimated in 73 patients of both sexes (age range 2 to 73 years) with muscular dystrophy. Of the 73 patients, 43 had acute muscular dystrophy (childhood or pseudohypertrophic type) and 30 had the chronic disease (adult slowly progressive or myotonic variety). A control group of 79 male and 32 female student volunteers was also studied. No changes were found in the serum levels of 5-nucleotidase and ATPase in patients with either type of dystrophy. In patients with the acute condition serum levels of MDH, GOT, GPT, LDH, and aldolase were all increased to values ranging from 3 (MDH) to 10 (aldolase) times the normal. Patients with chronic dystrophy showed normal or slightly raised levels of the transaminases, dehydrogenases, and aldolase. These results confirm earlier findings by other workers [see Dreyfus et al., *Ann. N.Y. Acad. Sci.*, 1958, 75, 235].

R. Rodnight

853. Observations on Essential Tremor

J. MARSHALL. *Journal of Neurology, Neurosurgery and Psychiatry [J. Neurol. Neurosurg. Psychiat.]* 25, 122-125, May, 1962. 4 figs., 8 refs.

BRAIN AND MENINGES

854. **The Kleine-Levin Syndrome: Hypersomnia, Bulimia, and Abnormal Mental States**

A. GALLINEK. *World Neurology [Wld Neurol.]* 3, 235-243, March [received June], 1962. 17 refs.

The Kleine-Levin syndrome is the term which has been applied to the episodic occurrence of states of excessive hunger (bulimia) and of excessive sleep (hypersomnia) in association with fluctuating psychiatric symptoms. These symptoms are variable, ranging from clouding of consciousness or amnesia to classic depressive features. Usually there are also signs of gastro-intestinal and other autonomic disturbances, such as hyperhidrosis, pilomotor erection, acrocyanosis, and yawning. Occasionally there is polydipsia. A preceding infectious illness is frequent but not the rule. During the periods of excessive sleep the electroencephalogram shows a normal sleep record.

In this paper from the Columbia-Presbyterian Medical Center, New York, 3 typical and 2 borderline cases are described. In one of these there were features of narcolepsy and cataplexy in addition to the Kleine-Levin syndrome which served to demonstrate the relationship between the syndrome and narcolepsy. The author states that a hypothalamic location of the syndrome is justifiable and that the reticular activating system must also be taken into account because of its effect on wakefulness and muscle tone.

The literature on the syndrome is briefly reviewed.

J. MacD. Holmes

855. **Psychologic Aging as a Pre-existing Factor in Strokes**

A. GRUEN. *Journal of Nervous and Mental Disease [J. nerv. ment. Dis.]* 134, 109-116, Feb. [received May], 1962. 15 refs.

In an attempt to determine whether subjects "who have suffered strokes are more like older persons in their cognitive and affective functions" the author compared a group of 36 ambulatory patients who had had a stroke and were attending the follow-up clinic at Bellevue Hospital, New York, with a group of 30 retired men and women without a history of a stroke. The group who had had a stroke included 20 males, aged 51 to 79 years (average 64.5 years), and 16 females, aged 40 to 70 years (average 57.3 years). The control group contained 15 males, aged 66 to 80 years (mean 71.3 years), and 15 females, aged 59 to 85 years (mean 70 years). Both groups were subjected to the following: (1) the block design test of the W.A.I.S. [Wechsler Adult Intelligence Scale], to test abstract verbal thinking; (2) the comprehension subtest of the W.A.I.S., to measure judgment and comprehension of social values and situations; (3) the information subtest of the W.A.I.S., for educational level and to provide a basis for testing functional efficiency on the other tests; (4) Cattell's perseveration test, relating to flexibility in re-adapting elements of old habits to new ones; (5) Secord's body-cathexis test; (6) the Rorschach test; and (7) the index of motor and sensory impairment.

The most important findings were: (1) the "likeness" in personality structure between experimental and control groups and (2) the lack of relationship between the behaviour measured and the degree of motor and sensory impairment. With regard to (1) the author considers that the younger experimental group resembled not only older normal people but even people with early presenile changes. He is

[logically] led to propose the thesis that the features which made the experimental group similar to the controls were present before the stroke—in other words, that a psychological "ageing" process pre-dates the occurrence of the stroke. This may be only a concomitant to the factors producing strokes, but it may also be an early manifestation of cerebral vascular disease.

Rex Matthews

856. **The Relationship of Subdural Hematoma to Anticoagulant Therapy**

L. M. WIENER and M. NATHANSON. *Archives of Neurology [Arch. Neurol. (Chic.)]* 6, 282-286, April, 1962. 16 refs.

Subdural haematoma sometimes complicates anticoagulant therapy, although the incidence of this complication is not known. It is easier to determine the frequency of previous anticoagulant therapy in patients with proved subdural haematoma. At Mount Sinai Hospital, New York, in the 5-year period 1956-60 a diagnosis of subdural haematoma was established in 50 patients by angiography, surgery, or necropsy, and in 6 of these a history of anticoagulant therapy during the preceding months was obtained. A 7th case from another hospital is included in the present series. The clinical course of the condition in these patients did not differ from that found among those who had not received anticoagulants, apart from the fact that the former were, on the average, 8 years older than the latter. Data on the prothrombin time at the presumed onset of the haemorrhage were inadequate for full evaluation, but it appeared that bleeding usually occurred in the presence of a therapeutic rather than an excessively high level of anticoagulation. A history of trauma was obtained in only 2 of the 7 patients who had received anticoagulants, compared with 30 of the 44 who had not. Three of the 7 anticoagulant-treated patients died, compared with 15 of the 44 who had not been given anticoagulants. Necropsy on these 3 patients showed no evidence of bleeding elsewhere in the brain.

Bernard Isaacs

857. **Post-traumatic Subdural Hematoma: Further Observations on Nonsurgical Treatment**

C. AMBROSETTO. *Archives of Neurology [Arch. Neurol. (Chic.)]* 6, 287-292, April, 1962. 10 figs., 7 refs.

From the Department of Neurology, University of Bologna, comes this report of 3 patients with chronic subdural haematoma who have been successfully treated non-surgically. The patients were men, aged 47, 57, and 58 respectively, who had sustained minor head injuries some 2 or 3 months before admission and who had developed signs and symptoms of widespread and progressive neurological impairment. Haematoma formation was demonstrated by angiography, and the patients were treated by rest in bed, diet, antihaemorrhagic and vasoprotective [*sic*] drugs, corticosteroids, and intravenous injections of hypertonic glucose solutions. All 3 patients showed complete clinical recovery, accompanied by angiographic evidence of resolution of the haematoma.

In discussing the possible mechanism of recovery the author refers to the observation that in this age group and at this stage of illness it is common to find defibrination of the blood of the haematoma with little or no membrane formation, conditions which would favour the success of such measures as infusions of hypertonic fluids. He also suggests that in his patients bleeding may have occurred from arteries

and capillaries running between the two layers of dura rather than from the veins, and he feels that such an "intradural" haematoma may be more benign than a true subdural one. In conclusion the author emphasizes that whatever the future place of medical treatment proves to be, operation must be instituted promptly in those cases of subdural haematoma in which there are severe and progressive signs of raised intracranial pressure, and in those with signs of uncal herniation.

Bernard Isaacs

858. Acute Pneumococcal Meningitis. The Significance of Mechanical Factors in Influencing Mortality

P. W. HUTTON, A. G. SHAPER, and A. M. M. WILSON. *Transactions of the Royal Society of Tropical Medicine and Hygiene [Trans. Roy. Soc. trop. Med. Hyg.]* 56, 149-155, March, 1962. 12 refs.

The results are reported from Makerere College Medical School and Mulago Hospital, Kampala, Uganda, of the treatment of 24 cases of acute pneumococcal meningitis in which the diagnosis had been established by culture. The ages of the patients, all Africans, ranged from 6 to 60 years; the majority were young adults. Patients were allocated at random to treatment by either (1) one mega unit of penicillin intramuscularly 2-hourly for 5 days, or (2) one mega unit of penicillin intramuscularly 2-hourly for 5 days with prednisone by mouth, the dosage of the latter being 80 mg. on the first day, 40 mg. on each of the second and third days, and 20 mg. on each of the fourth and fifth days. The mean penicillin level in the cerebrospinal fluid during treatment was 1 unit per ml. and this was usually reached 4 to 8 hours after the first injection. Of the 9 patients given penicillin alone 4 died, and of the 15 patients treated with penicillin and prednisone 6 died.

The results were compared with those of two earlier trials. In the first of these (A) the patients were given 20,000 to 30,000 units of penicillin daily by intrathecal injection, 50,000 to 100,000 units of penicillin a day intramuscularly, and a sulphonamide every 4 hours by mouth. The patients in the second trial (B) received 100 to 200 mg. of chloramphenicol per kg. body weight by mouth in 24 hours. In both trials the diagnosis was based on the findings on examination of a stained film of the cerebrospinal fluid. The results obtained by the present authors were significantly better than those of trial A, but not significantly better than those of trial B. The number of cases was too small to permit a comparison between the efficacy of penicillin and that of penicillin with prednisone. According to the authors, the state of consciousness is the most important feature in prognosis, and intracranial mechanical factors may be responsible for many deaths. Lumbar puncture may therefore be dangerous; it should be done with a fine needle and only the minimum quantity of cerebrospinal fluid required for diagnosis should be removed.

P. T. Main

859. The Effect of Chlordiazepoxide on the Electroencephalogram. [In English]

P. M. JEAVONS. *Epilepsia [Epilepsia (Amst.)]* 3, 110-116, March [received May], 1962. 2 figs., 4 refs.

At All Saints Hospital, Birmingham, chlordiazepoxide was given to 41 patients suffering from epilepsy of various types; it was given in addition to regular anticonvulsants in those cases in which these were employed. The electro-

encephalogram (EEG), which was recorded before and after a period of treatment lasting one month or longer, showed that the drug had an effect on the abnormal EEG. In 17 cases paroxysmal discharges were reduced and in 18 cases there was an increase in normal alpha activity. A reduction in background slow activity was observed in 23 cases and an increase in fast activity in 24. Clinical effects were found to be unpredictable and showed no close correlation with improvement in the EEG.

J. B. Stanton

860. EEG and Clinical Study of Epilepsy during Maturation in Man. [In English]

P. PASSOUANT and J. CADILHAC. *Epilepsia [Epilepsia (Amst.)]* 3, 14-43, March [received May], 1962. 19 figs., bibliography.

A study of the clinical and electroencephalographic (EEG) aspects of epilepsy was undertaken in an attempt to delineate the effects of maturation and to obtain information on the evolution of epileptic manifestations appearing at different ages. It was found that convulsions in the newborn depend on focal discharges in the hippocampal structures and represent the "archetype" of epilepsy. Generalized epilepsy in children manifests itself by convulsions, by tonic spasms and tonic seizures with hypsarrhythmia, by isolated tonic spasms, or by akinetic attacks. The bilaterally synchronous wave-and-spike dysrhythmia of petit mal is the expression of centrencephalic epilepsy in the child between the ages of 3 years and puberty. Focal attacks are also considered together with the evolution of discharging EEG foci in late childhood. The authors state that the polymorphism of clinical and EEG symptoms of epilepsy during the course of maturation is clear and discrepancies are often found—for example, centrencephalic epilepsy may be manifested clinically by Jacksonian attacks, and a focal discharge by a generalized convulsion of abrupt onset. This study indicates successive stages in the organization of the clinical and EEG patterns of epilepsy between infancy and adult life.

J. B. Stanton

861. Non-Jacksonian Hemiconvulsive Seizures. One-sided Generalized Epilepsy. [In English]

H. GASTAUT, J. ROGER, J. FAIDHERBE, S. OUAHCHI, and G. FRANCK. *Epilepsia [Epilepsia (Amst.)]* 3, 56-68, March [received May], 1962. 2 figs., 8 refs.

The distinction between unilateral convulsions and Jacksonian seizures is discussed. In children the former are much more common than the latter and may take the form of unilateral grand mal or hemiclonic seizures or both. In these cases the electroencephalographic abnormality during an attack arises from the contralateral hemisphere. These unilateral seizures represent the principal type of seizure in very young children and may occur in the absence of any organic cerebral lesion, from lowering of the convulsive threshold by hypocalcaemia, hyperthermia, or dehydration. In some cases prolonged and intense hemiconvulsions may cause oedema of the hemisphere with uncal herniation leading to vascular compression and ischaemia which may be responsible for a residual chronic epilepsy of true organic origin. The physiopathology of these seizures is discussed. Clinically the presence of these non-Jacksonian hemiconvulsive seizures is regarded as a contraindication to any type of surgical intervention, including hemispherectomy.

J. B. Stanton

Psychiatry

862. Psychic State and Adrenocortical Function: a Psychophysiological Study of Emotion

N. SUWA, I. YAMASHITA, H. OWADA, S. SHINOHARA, and A. NAZAZAWA. *Journal of Nervous and Mental Disease (J. nerv. ment. Dis.)* 134, 268-276, March [received May], 1962. 6 figs., 32 refs.

In this paper from Hokkaido University School of Medicine, Japan, is reported a continuation of a psychophysiological research study which was started in 1953. The conclusions reached so far are: (1) neurotic and psychotic patients show various kinds of physiological extremes rarely found in healthy subjects; (2) these abnormal values are not necessarily related to diagnostic entities, but are usually bodily consequences of emotional disturbances common to all types of psychiatric illness; and (3) in deteriorated schizophrenic subjects physiological changes have a specific pattern.

The present authors have studied adrenocortical activity in relation to mental disorder in 44 subjects, including healthy persons, psychoneurotics, schizophrenics, and manic depressives. Indices of adrenocortical activity were the circulating eosinophil count, urinary excretion of hydroxycorticoids, and uropepsin content of the urine. Studies were both transverse and longitudinal in time.

In healthy subjects the blood eosinophil count and the urinary excretion of 17-hydroxycorticoids and of uropepsin were usually constant from day to day. In psychoneurotic patients fluctuations in these indices were synchronous with changes in the emotional state. Disturbed and deteriorated schizophrenic patients showed wide fluctuations in these values, a result qualitatively different from that in healthy subjects and psychoneurotic patients. It is suggested that this is due to a defect in the maintenance of homeostasis of the entire body. The authors consider that further research is needed before conclusions can be drawn.

B. M. Davies

863. A Psychological Basis for Indifference to Pain

S. F. SCHNEIDER. *Psychosomatic Medicine [Psychosom. Med.]* 24, 119-132, March-April, 1962. 15 refs.

The author reports, with clinical details, an investigation of 3 male patients aged 56, 42, and 67 years respectively, who displayed indifference to pain stimuli. The study was carried out at the University of Michigan Medical Center, Ann Arbor. The 3 patients had a number of psychological characteristics in common. Thus they all regarded their pain insensitivity as an index of masculine prowess and were disdainful of others who responded to pain. Denial mechanisms were prominent and the patients had a narcissistic sense of invincibility. Although they did manifest an overcompensatory concern for others in some respects, their object relations were on the whole impaired, and they applied themselves with inordinate energy to their employment. Their insensitivity to pain was accompanied by a diminution of pleasurable bodily feelings.

A massive use of denial beginning in early childhood may in theory explain the indifference to pain, but the lack of

gross psychopathology in the present patients does not support this view. Conversion hysterical mechanisms likewise provide an implausible explanation, since the duration and stability of the pain insensitivity were not in alignment with hysterical phenomena. The author suggests that the most credible hypothesis is that indifference to pain arises through the regressive reactivation of the denial mechanism under the impact of Oedipus-type conflicts. He considers that there is a need for further study of this syndrome, especially by means of psychoanalytic techniques.

A. Balfour Sclaire

864. A Controlled Trial of Trifluoperazine in the Treatment of the Mentally Subnormal Patient

D. S. SHARPE. *Journal of Mental Science [J. ment. Sci.]* 108, 220-224, March [received May], 1962. 8 refs.

Aggression and antisocial conduct are often displayed by mentally subnormal patients. This report from Botleys Park Hospital, Chertsey, Surrey, describes a trial of trifluoperazine in 30 female mentally subnormal patients aged between 13 and 57 who showed severe behaviour disorder, and of whom 6 had grand-mal epilepsy. Half the patients received trifluoperazine in a dosage that reached 30 mg. per day divided into 3 doses over 3 months; the others received a placebo.

Assessment was made by two ward sisters using the Claridge Excitability Rating Scale, which assesses all aspects of the behaviour of patients of this type. This showed that there was a statistically significant improvement in the group receiving trifluoperazine, only 4 of these patients failing to improve. There were no toxic reactions, though Parkinsonian symptoms were common. No change was noted in the mental age of the patients during the 3 months of the trial.

B. M. Davies

865. A Trial of Tetrabenazine ("Nitoman") in Disturbed Mentally Subnormal Patients

G. C. KANJILAL and B. MATHESON. *Journal of Mental Science [J. ment. Sci.]* 108, 225-228, March [received May], 1962. 8 refs.

Tetrabenazine ("nitoman") is one of a new series of benzoquinolizin compounds and has central actions similar to those of reserpine, but it acts more quickly and has a shorter duration of activity. For the present trial, carried out at South Ockenden Hospital, Essex, 20 subnormal patients were selected who because of restlessness and aggression were a problem in ward management. They were given tetrabenazine (150 mg. daily) and reserpine (1.5 mg. daily) using a cross-over, double-blind technique, the period of treatment with each drug lasting for 6 weeks. Assessment was made clinically by the doctor and nursing staff. The results showed that the effects of tetrabenazine were similar to those of reserpine, though the absence of lethargy or depression with the former was notable. Tetrabenazine also produced improvement more rapidly and caused only minor side-effects. It appears to be a potentially useful drug in selected cases.

B. M. Davies

866. The "Target" Symptoms in the Treatment of Depressions

J. LOPEZ-IBOR. *Comprehensive Psychiatry* [Comprehens. Psychiat.] 3, 15-19, Feb. [received April], 1962. 8 refs.

The author of this paper from the University of Madrid discusses the symptoms of depression which should be regarded as key and nuclear to the disease on the basis of his experience in the treatment of 125 cases with imipramine. He mentions the classifications of Lehmann and of Cameron, but suggests that since Freyhan obtained his best results with imipramine in the manic-depressive group, the view of Schneider that in endogenous depression "vital sadness" is the nuclear symptom should be considered. This being located in the "corporeal ego" the state of sadness is projected into the soma, and it is logical to expect a response to somatic treatment.

Of the author's 125 "depressives" 51% responded to imipramine, but the remission rate was 84% in those with "vital sadness". Discussing these results he states that it remains difficult to assess the presence or degree of "vital sadness" since the patient's description is not an infallible guide; other symptoms such as "guilt delusions" may obscure the mood disorder. In spite of evident "vital sadness", some patients may not respond because they are not in a suitable phase of their illness, or again, the secondary influence of imipramine on the vegetative functions may be unfavourable—for example, in marked vagotonia, as shown by the response to a modification of Funkenstein's test.

It is concluded that imipramine is effective in the treatment of the nuclear symptom of depression, the "vital sadness". This sadness is somatotropic or somatogenic, and the more it manifests itself in the clinical picture the better the therapeutic results.

R. P. M. Urquhart

867. Schizophrenia on Duty

T. M. BADGLEY, H. C. HOLLOWAY, and J. L. HEDLUND. *American Journal of Psychiatry* [Amer. J. Psychiat.] 118, 916-920, April, 1962. 1 fig., 15 refs.

During the 3 years 1956-58 schizophrenic reaction was diagnosed (according to the diagnostic standards of Bleuler) in 784 male military patients at the Walter Reed General Hospital, Washington. After treatment (which included psychopharmacological agents, electric convulsion therapy, individual and group psychotherapy, recreational therapy, and occupational therapy) 201 (25.6%) of the 784 patients were returned to duty, 524 (66.8%) were discharged from the service, and 59 (7.5%) were otherwise disposed of.

The 201 who returned to duty included 19 officers and 182 other ranks; their length of service ranged from 2 days to 19 years (mean 6.8 years), their ages from 17 to 49 (mean 27.9) years, and their length of education from 4 to 20 (mean 11.2) years; 55 were negroes; 103 were unmarried. The schizophrenic reaction was of paranoid type in 61%, catatonic in 4%, latent in 6%, and mixed in 28%. In all cases except those of latent type the condition had been acute in onset; in 10% it was assessed as mild, in 33% as moderate, and in 50% as severe. Clinical records indicated a prepsychotic schizoid pattern in 18%, chronic or recurrent acting out in 8%, and chronic or recurrent neurotic symptoms in 6%. Possible precipitating factors were found in 27%.

Two years after their return to duty 132 (65%) of the 201 men had been discharged from the service—66 on account

of relapse or other decompensation, 13 because of low intelligence or reasons other than schizophrenia, and 53 because their term of service had expired. Of the 69 (34%) who were still on active duty, 13 had been in hospital and 7 had undergone disciplinary action. These 69 men were significantly older than the others, with significantly higher rank, longer service, and more citations and awards, and more of them were married. Of 56 of these men on active duty when the report was written, unit commanders reported that 88% were average or above average in terms of effective work, motivation, emotional stability, and social adjustment.

The authors have not found a means of identifying the schizophrenic who will reintegrate.

G. de M. Rudolf

868. The General Practitioner and the Schizophrenic Patient

C. M. PARKES, G. W. BROWN, and E. M. MONCK. *British Medical Journal* [Brit. med. J.] 1, 972-976, April 7, 1962. 2 figs., 7 refs.

The resettlement of schizophrenic patients after their discharge from hospital is a particular interest of the Medical Research Council Social Psychiatry Research Unit at the Maudsley Hospital, London, from which this paper comes. The authors describe the services provided by the general practitioner and by psychiatric out-patient clinics in caring for 96 such patients during the first year after their discharge from 8 London mental hospitals. Most of the information about domestic conditions and treatment problems was obtained by a sociologist during a visit to each patient's home a year after his discharge, or earlier if he was readmitted to hospital during the year. At the time of the visit the psychiatrist reviewed the clinical notes and discussed the case with the practitioner.

Of the 96 patients, 85 were seen either by a general practitioner or at a clinic during the year; 46 attended both. Although practitioners saw a majority (70) of the patients, most of the visits were for repeat prescriptions and occupied little time. Drug treatment was usually initiated by the psychiatrist at the time of the patient's discharge; when initiated by the practitioner it was generally because the patient had had a relapse. The practitioners prescribed major tranquillizers less frequently and in lower dosage than did the clinics. Most of the work concerning relapses—admissions, referrals, home visits—fell to the practitioner.

Detailed inquiry revealed that 53 of 120 courses of drug therapy prescribed were probably not taken as intended and that 26 such courses were terminated within a month of discharge. When administration was supervised by a relative the failure rate was low (18% of 17 patients so supervised as compared with 54% of 56 patients not so supervised). The complaint made by most practitioners was of lack of liaison between the psychiatric services and themselves. Other complaints were of absence or inadequacy of discharge letters, premature discharge, and lack of home visits by psychiatric social workers. Patients' and relatives' comments were often directed against the general practitioner, and included criticism of his attitude and of his ability to deal with psychiatric disorders.

The authors consider that the general practitioner plays an important part in the care of schizophrenic patients after their discharge from hospital, and that he will perhaps prove to be the most suitable person to supervise and assist in resettlement. Closer cooperation with the relatives is

advocated, and improved liaison between psychiatrist and practitioner will be to their and the patient's advantage.

Alan A. Black

TREATMENT

869. Some Characteristics Common to Electroconvulsive Therapy and Prefrontal Leucotomy and Their Bearing on the Mode of Action of the Two Treatments

M. ROTH and R. GARSIDE. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 221-230, April, 1962. 2 figs., 20 refs.

The authors of this paper from the University of Durham point out that while the usefulness of electric convulsion therapy (E.C.T.) is most firmly established in the treatment of endogenous depression, the procedure is also of clinical value in certain confusional and schizophrenic states and neurotic conditions. Since E.C.T. does not affect the specific causes of these illnesses, it is not surprising that the relapse rate is relatively high. Relapses are particularly common if the treatment is stopped as soon as symptoms are in abeyance, and it is best to continue it for a time beyond this point. However, no objective method for determining when E.C.T. should be terminated has yet been found.

The most striking and sustained physiological changes brought about by E.C.T. are those in the electroencephalogram (EEG). They can be correlated, to some extent, with the clinical changes. These EEG phenomena can be studied more readily if a standard dose of thiopentone is given within a few hours of the treatment. Delta activity is elicited by this injection and a peak value is usually seen after about the fifth convulsion, although the rate of development of the peak varies. The relapse rate has been shown to be correlated with the amount of slow activity produced in the EEG. The EEG changes, which are particularly marked in the frontal areas, are probably due to alteration in the activity of the diffuse projection system. The authors speculate whether the effects of E.C.T. and the effects of prefrontal leucotomy have certain factors in common. The similarity in the effects of the two procedures may, they suggest, be due to a common site of action—namely, the frontal lobes and the thalamofrontal connexions. The ways in which action on the thalamofrontal system could influence psychiatric illness are discussed. It may be that in the affective and schizophrenic psychoses, physical treatments such as E.C.T. and leucotomy act by interfering with certain cerebral mechanisms which serve to sustain and to perpetuate the neuronal activities underlying these illnesses.

B. M. Davies

870. A Controlled Comparison of Imipramine and Electroplexy

A. A. ROBIN and J. A. HARRIS. *Journal of Mental Science* [*J. ment. Sci.*] 108, 217-219, March [received May], 1962.

At Runwell Hospital, Wickford, Essex, 31 depressed patients clinically suitable for electric convulsion therapy (E.C.T.) were treated in random order with either E.C.T. (15 cases) or imipramine (16 cases); the two groups of patients were comparable. Assessment of the results was made by a physician who was unaware of the treatment given. Of the 14 patients receiving E.C.T. who completed the trial 12 showed marked or moderate improvement, compared with only 3 of the 12 imipramine patients completing the trial; of these latter 12, moreover, 11 subsequently required E.C.T.

B. M. Davies

871. Iso-carboxazid ("Marplan") in Depressive States. (L'isocarboxazide (Marplan) dans les états dépressifs).

G. BOUDIN and A. LAURAS. *Thérapie [Thérapie]* 17, 255-272, March-April, 1962.

"Marplan" (isocarboxazid) is a monoamine oxidase inhibitor related to iproniazid. At the Saint-Antoine Hospital, Paris, the authors carried out a trial in 90 cases of depression (33 male and 57 female), excluding cases associated with schizophrenia. There were two groups: (1) 44 patients followed up by one observer in private practice and (2) 46 patients treated in a psychiatric out-patient department. All varieties of depression were represented. Dosage in Group 1 tended to be lower than in Group 2, with better tolerance. Physical side-effects were few; hypotension was observed but never led to serious symptoms or cessation of treatment. In Group 2 there were instances of loss of consciousness, with cerebral vascular accident in one arteriosclerotic patient. Apart from this there were no neurological abnormalities, and no example of the paroxysmal hypertension noted with other thymoleptic drugs. Normal sleep returned in most cases, and improvement in libido was noted in one or two cases. Many patients gained weight and had better appetites. There were no digestive disturbances and no clinical evidence of liver damage. Undesirable psychological side-effects were few: a paranoid disturbance, excessive mood swing in a manic depressive (possibly coincidental), transient anxiety, and one attempted suicide. Where improvement began, depression and anxiety disappeared first, and this was followed by increased interest in the surroundings and in social activities. Ten to 40 days intervened between the start of treatment and signs of improvement, which then continued for up to 2 months. Doses above 40 mg. a day increased the risk of intolerance without necessarily speeding the cure. The minimum initial effective dose was 20 mg. per day. The usual maintenance dose was 10 mg. per day.

Biochemical tests were not performed on all the patients. When isocarboxazid had been given for over 6 months there were instances of hyperbilirubinaemia, suggesting a cholestatic effect similar to that produced by chlorpromazine, although further study would be needed to confirm this. More serious were the abnormal results of a number of late flocculation tests, indicative of liver cell damage, but without clinical signs. These reactions did not appear before 6 months and the authors advise caution, since all iproniazid drugs can damage the liver if given for long periods. No plasma electrolyte disturbance was noted; there were a few cases of transient increase in the urinary potassium content which seemed to have no significance.

The results in Group 1 were undoubtedly superior to those in Group 2, and this is ascribed to closer control and longer observation. Endogenous and neurotic depression responded best, although some improvement was obtained in the organic reaction types. The results in both groups combined showed decided benefit in half, partial success in a quarter, and little improvement in a quarter. There was no significant relationship between the size of the dose and the result. Success was obtained in several cases in which previous treatment, including imipramine and nialamide, had failed. Patients who had received other thymoleptics all preferred isocarboxazid. The authors consider that out-patient treatment should be reserved for cases in which there is no risk of suicide.

Gavin Thurston

Dermatology

872. Skin Protection Afforded by Ointments

G. K. STEIGLEDER and W. P. RAAB. *Journal of Investigative Dermatology* [J. invest. Derm.] 38, 129-131, March [received May], 1962. 12 refs.

The authors have investigated, at Columbia University, New York, the protection afforded against external irritants by 8 different types of ointment applied to the skin. Their method was based on the power of the skin esterases to hydrolyse α -naphthylacetate and liberate α -naphthol which can then combine with the dye diazo blue B. The resulting azo-dye stains the skin. A total of 86 healthy male and female subjects took part in the trial. It was found that white petrolatum U.S.P. (white soft paraffin B.P.) gave the best protection and that this was not enhanced by the addition to it of silicone.

John T. Ingram

873. Angiokeratoma Corporis Diffusum: a Clinical Study of Eight Affected Families

D. WISE, H. J. WALLACE, and E. H. JELLINEK. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 177-206, April, 1962. 18 figs., bibliography.

After reviewing the literature relating to angiokeratoma corporis diffusum from its first description in 1898, the authors describe a study of the condition in 8 British families in which 21 individuals were affected. Analysis of the families shows that the gene is sex-linked, with occasional penetrance in the heterozygous female and constant penetrance in the homozygous male subject.

The individual lesions of angiokeratoma corporis diffusum are punctate, blood-filled cavities, up to 4 mm. in diameter, situated in the superficial layers of the skin. The surface is shiny, hemispherical in shape, and dark red in colour. Clusters of lesions are characteristic, especially on the lower trunk and thighs. The differential diagnosis is discussed.

The most lethal manifestation of the disease is renal failure, due to damage to the renal parenchyma or other changes. Proteinuria usually develops in the 2nd decade, and uraemia in the 4th or 5th decade. The chronic oedema of the legs present in most patients appears without hypoproteinaemia. Varicose veins, hypochromic anaemia, premature coronary arterial disease, strokes in early life from cerebrovascular disease, varicosities of the retinal veins, pain in the extremities, and mild arthropathy of the terminal interphalangeal joints are other concomitant manifestations. The average age of male patients at death was 42 years (range 30 to 54 years).

S. T. Anning

874. Chronic (Lupoid) Leishmaniasis

J. H. S. PETTIT. *British Journal of Dermatology* [Brit. J. Derm.] 74, 127-131, April, 1962. 7 figs., 10 refs.

A study of 68 cases of chronic dermal leishmaniasis seen in the Shiraz province of Iran is reported. The lesions, which had been present for at least 8 years, seemed to have begun as ordinary oriental sores, the scar later presenting a varied clinical picture, the commonest being almost indistinguishable from that of lupus vulgaris. While smears from an acute oriental sore abound with Leishman-Donovan bodies and culture produces large numbers of the lept-

monad form, great difficulty is experienced in seeing and growing organisms from lesions from the chronic type of case. Nor can much help be obtained from the histopathology of the lesion, which is similar to that of tuberculosis or tuberculoid leprosy. The most reliable aid to diagnosis is probably the history given by the patient of the onset as a typical oriental sore. The condition proved resistant to forms of treatment usually recommended.

E. W. Prosser Thomas

875. Disseminated Anergic Cutaneous Leishmaniasis

J. CONVIT, F. KERDEL-VEGAS, and B. GORDON. *British Journal of Dermatology* [Brit. J. Derm.] 74, 132-135, April, 1962. 2 figs., 8 refs.

A case of an unusual type of leishmaniasis characterized by papules, nodules, and plaques spread over most of the body is reported from Vargas Hospital, Caracas, Venezuela. The condition may be confused with lepromatous leprosy, sarcoidosis, or xanthoma tuberosum. Abundant parasites are seen in smears. The lesion is a specific granuloma thought to be due to a special strain of *Leishmania brasiliensis*. The patient in the present case showed a good initial response to an antimony compound, but it was expected that many of the lesions would recur.

E. W. Prosser Thomas

876. The Metabolic Response to Exfoliation

I. M. FREEDBERG and H. P. BADEN. *Journal of Investigative Dermatology* [J. invest. Derm.] 38, 277-284, May, 1962. 5 figs., 17 refs.

The metabolic response to scaling in exfoliative dermatitis was studied in 3 patients at the Massachusetts General Hospital, Boston. For collection of the scales each patient wore a one-piece garment which left only the face exposed. Patients were given a constant diet of calculated composition containing 25 Calories per kg. body weight and 1 g. of protein per kg. A correlation was observed between the degree of scaling and the extrarenal water loss, so that measurement of intake and output served as a method of following the course and therapeutic response. The authors state that exfoliation may reach high levels, over 17 g. per square metre a day, without clinical or laboratory evidence of negative nitrogen balance.

John T. Ingram

877. Histochemically Demonstrable Carbohydrates of Appendageal Tumors of the Skin. II. Benign Apocrine Gland Tumors

R. M. FUSARO and R. W. GOLTZ. *Journal of Investigative Dermatology* [J. invest. Derm.] 38, 137-142, March [received May], 1962. 15 figs., 13 refs.

Following the technique used at the University of Minnesota, Minneapolis, in their several previously described studies the authors have applied their histochemical staining with alcian blue and periodic-acid-Schiff to a study of the apocrine glands, naevus syringocystadenomatosus papilliferus, and dermal cylindromata. From their study of the carbohydrates in these tumours they conclude that they are related to apocrine glands, a finding which supports the views of Lever and others.

John T. Ingram

Paediatrics

878. Oesophageal Atresia: Tracheo-oesophageal Fistula. A Study of Survival in 218 Infants

D. J. WATERSTON, R. E. BONHAM CARTER, and E. ABERDEEN. *Lancet* [*Lancet*] 1, 819-822, April 21, 1962. 10 figs., 10 refs.

This is a report on 218 infants with oesophageal atresia treated at the Hospital for Sick Children, Great Ormond Street, London, from 1946 to 1959. All but one had an operation. The anomaly presented in 7 different ways. In the common type (186 cases, or 85%) the upper oesophagus ended in a blind pouch and the lower oesophagus joined the respiratory tract near the tracheal bifurcation. A rare variant of this deformity (4 cases) had, in addition, no lumen of the lower oesophageal portion near the trachea. Oesophageal atresia without tracheo-oesophageal fistula occurred in 19 (9%); in all but 2 there was a wide gap between the oesophageal ends. Atresia with tracheo-oesophageal fistula to the upper oesophagus was found in 2 cases and fistulation of upper and lower ends in 3. Tracheo-oesophageal fistula without atresia occurred in 3 cases. The remaining case was a variant of the foregoing types.

Exactly half (109) of the infants survived operation in that they left hospital taking feeds normally. The deaths depended upon 3 main factors. The first of these was birth weight: when this was under 4 lb. (1.814 kg.) survival was most unlikely, whereas most of the babies who weighed over 5½ lb. (2.494 kg.) at birth survived. The second factor was additional congenital anomalies: when these were severe survival was unlikely whatever the birth weight, but where there was no additional anomaly 75% of the babies survived. The third factor was lung complications, particularly pneumonia, collapse and consolidation. On this basis classification into 3 groups is suggested: Group A—over 5½ lb. birth weight and well. Group B—(1) birth weight 4 to 5½ lb. and well; (2) higher birth weight, moderate lung complication and congenital anomaly. Group C—(1) birth weight under 4 lb.; (2) higher birth weight and severe lung complication and severe congenital anomaly. This classification has been applied to 113 cases treated between 1951 and 1959.

Primary anastomosis was attempted in all cases unless clearly impossible. Of 38 babies in Group A, 36 survived; of 43 in Group B, 29 survived; and of 32 in Group C, only 2 survived. It is therefore recommended that in Group C babies primary oesophageal anastomosis should not be attempted, but that gastrostomy and perhaps cervical oesophagostomy be performed with oesophageal anastomosis or a colonic transplant at a later date.

Andrew M. Desmond.

879. Embryopathies Resulting from Maternal Rubella. (Эмбриопатии, связанные с краснухой)

H. S. MARTINSON. *Вопросы Охраны Материнства и Детства* [*Vop. Okhrany Materin. Dets.*] 7, 67-69, April, 1962. 12 refs.

The author has collected evidence from many sources concerning the relationship of rubella in the expectant mother to developmental defects in the foetus. L'Etang (1882) ascribed congenital cataract in infants to this cause. Gregg (1941) observed 13 newborn infants with congenital cataract

whose mothers had contracted rubella in the first 2 months of pregnancy, and other infants who in the same circumstances suffered from deafness or congenital heart disease. Other eye defects found included macrophthalmia (associated in 60% of cases with cataract), iridocyclitic defects, retinitis pigmentosa, glaucoma (often with buphthalmia), primary optic atrophy, and corneal ulceration. Gregg and Winterbotham described auditory nerve deafness in 70% of cases. The cardiac defects reported included patent ductus arteriosus and atrial and ventricular septal defects. Evans found delayed eruption of teeth, with malformation and a tendency to early caries. Swann found skull deformities, including microcephaly, macrocephaly associated with hydrocephalus, and platycephaly, in 50% of cases. Mental abnormality, ranging from anorexia nervosa and disturbed sleep rhythm to complete idiocy, has been a common finding. Cases of athetosis, epileptiform attacks, spastic paraplegia, and unilateral cortical atrophy are described. Lamy and Seror (1959) reported the results of a questionnaire concerning over 100,000 births in the Seine department of France: of 48 mothers who had contracted rubella in the first 20 weeks of pregnancy, 50% gave birth to children with congenital defects, chiefly cardiac; of 283 mothers who had been exposed to rubella but showed no clinical evidence of having contracted it, 2 had children with congenital defects; of 571 mothers known neither to have had contact with rubella nor to have contracted it, 4% had stillbirths but no congenital defects were reported. Greenberg and Pellitteri (1957) found a lower percentage of embryopathies following rubella (12%), but 40% of their patients aborted.

These findings show the importance of shielding the expectant mother from exposure to rubella, at least during the first half of pregnancy. Coffey and Jessop (*Irish J. med. Sci.*, Jan., 1959; *Abstr. Wld Med.*, 1959, 25, 447) concluded that the risk of embryopathy was 10 times the normal in women who developed rubella and 2½ times the normal in women who had been in contact with cases of the disease. The severity and the site of the congenital defect vary with the stage of gestation at which the disease occurs, the most serious cases being those in which the foetus is in the second to the ninth week. There is little risk after the end of the fifth month. Should exposure take place, prophylactic injection of the serum of convalescents is recommended. Coffey and Jessop advise this precautionary measure in all pregnant women during an epidemic, but it is of little value once the mother has contracted the disease. Gamma globulin (immune) must be given not later than 72 hours after contact; its effect lasts only 18 days. L. Firman-Edwards

880. Gastrostomy for the Newborn Surgical Patient: a Report of 140 Cases

I. A. MEEKER and W. H. SNYDER. *Archives of Disease in Childhood* [*Arch. Dis. Childh.*] 37, 159-166, April, 1962. 3 figs., 3 refs.

The authors report 140 consecutive cases of prophylactic gastrostomy in newborn infants, without complications related to the operation, performed at the Children's Hospital, Los Angeles, between 1957 and 1961.

The management of nasogastric tubes in small babies is difficult and the prevention of inhalation of regurgitated gastro-intestinal content requires constant and skilled nursing. The use of gastrostomy tubes instead of nasogastric tubes is the subject of this report. Gastrostomy may usefully be performed in cases in which there is a risk of aspiration of gastric contents, or where reduction in gastro-intestinal distension, improvement in respiratory exchange, protection from evisceration, or facilitation of oral feeding is called for. The technique of gastrostomy is described and illustrated and an account is given of the management of the tube and of a method of giving nourishment through it. The tube is left *in situ* for 12 to 14 days and can be removed when the infant has become an out-patient. The opening closes spontaneously. Since continuous suction by means of a pump has been associated with a high incidence of blocking, it is advised that the gastrostomy tube be left open at all times and suction avoided, although in some cases the tube may be fitted to an underwater seal. The cases in which the authors used gastrostomy were: diaphragmatic defects (17), tracheo-oesophageal fistula and oesophageal atresia (66), duodenal obstruction (19), jejuno-ileal obstruction (19), colon obstruction (8), omphalocele (9), and biliary atresia (2). Of the 140 infants treated, 39 were premature (of whom 14 survived) and 101 were full-term (of whom 81 survived).

Andrew M. Desmond

CLINICAL PAEDIATRICS

881. **Clinical Picture and Course of Adenoviral Pneumonia in Children.** (Особенности клиники и течения аденовирусной пневмонии у детей)
L. G. МАМУКИНА. *Вопросы Охраны Материнства и Детства* [Vop. Okhrany Materin. Dets.] 7, 10-13, April, 1962.

This is a report of the clinical findings in 76 children suffering from adenoviral pneumonia. The virus, of the 7A type, was cultured from the blood and from nasopharyngeal smears. All the children were under 5 years of age and 45 were in their first year. In all except 15 the onset was acute and accompanied by pyrexia. The patients when admitted to hospital within 3 days of the onset were fairly severely ill. Cough was frequent and distressing, in some cases dry and painful and in others accompanied by copious mucoid sputum. Faucial hyperaemia, in some cases with mucous haemorrhages, was present in 49 patients, and 5 had membranous conjunctivitis. In the pyrexial cases, sweating of the face and head was profuse. Cyanosis of the nasolabial triangle was present in 31, while in 10 cyanosis was generalized. Dyspnoea was always severe. Appetite was poor, and in 25% of the cases the stools were loose and frequent. The percussion note over the chest was normal, but moist sonorous rales were audible over all lobes. The liver and spleen were palpable in many cases. Neurological signs were also common and included neck rigidity, Kernig's sign, neurovascular instability manifested by dermatographia, and, often, convulsions. In 45 children tachycardia was present, with dulling of the heart sounds. Electrocardiograms in 20 cases showed evidence of sinus tachycardia with prolonged systole and, in some instances, low and deformed R and T waves with displacement of S-T. In half the patients the leucocyte count was normal, while in 28 it was

slightly raised (10,000 to 15,000 per c.mm.); in 55 children there was some lymphocytosis and occasionally monocytosis. The erythrocyte sedimentation rate was not notably raised. One child died.

Treatment consisted in administration of sulphonamides, antibiotics, and vitamins, injections of plasma, glucose and saline, and gamma globulin, and oxygen as required. Convalescence was prolonged and there was a tendency to recrudescence after 2 to 3 weeks. Radiological evidence of lung changes persisted for 3 to 4 weeks. At that stage tonics, calcium chloride, blood transfusion, and other symptomatic therapy were given. L. Firman-Edwards

882. **Rhino-cytological Investigations in Adenoviral Infections in Children.** (Риноцитоскопические исследования при аденовирусной инфекции у детей)
Т. Я. ЛЯРСКАЯ и С. Г. СЕШК. *Вопросы Охраны Материнства и Детства* [Vop. Okhrany Materin. Dets.] 7, 14-18, April, 1962. 2 figs., 24 refs.

Examination of smears, stained by Romanovsky's method, from the nasal mucosa of 36 children suffering from adenoviral infections showed characteristic protoplasmic inclusions in the cytoplasm of the epithelial cells and at times in the nuclei of the cylindrical and prismatic cells. Similar inclusions were found in the epithelium of the respiratory tract of children who had died from such infections and in cells of the conjunctivae of cases of membranous conjunctivitis. These bodies cannot be distinguished from those found in influenza, but if considered in conjunction with the clinical features of the disease, may be of diagnostic importance. L. Firman-Edwards

883. **Pleuropneumonia due to Staphylococci in Infants.** (Staphylococcies pleuro-pulmonaires du nourrisson)
J. VIALATTE, LE TAN VINH, R. TESTARD, and H. DALAYEUN. *Archives françaises de pédiatrie* [Arch. franç. Pédiat.] 19, 137-175, Feb. [received May], 1962. 17 figs., bibliography.

In this paper from the Hôpital Saint-Vincent-de-Paul, Paris, 129 cases of staphylococcal pneumonia in infants collected between 1953 and 1960 are reported. That the disease is still serious is reflected in the high mortality of 40%. The emphasis is placed, not on detailed case histories or statistical analysis, but on the clinical grouping into curable and fatal cases. Of the 77 children cured, 37 had mixed pulmonary and pleural lesions, in 30 the lesions were predominantly pleural and in 10 predominantly pulmonary. The different varieties are fully described and discussed. In the fatal group death occurred early in the disease; in 14 cases it was ascribed to overwhelming infection with little or no clinical or pathological response, and in these the x-ray findings were relatively minimal, though diffuse and often bilateral disease was found at necropsy. Almost half the fatal cases were associated with pneumothorax, and there was a small group in which death was due to asphyxia following a sudden vomica.

Perhaps the best part of this paper is the section dealing with the pathological studies. Macroscopical and microscopical examination of sections suggests that the disease starts as a haemorrhagic pneumonia with infarction progressing to suppuration and necrosis and leading to abscess formation. The abscesses are usually small, multiple, and scattered in one or more lobes; the danger lies in spread to the pleura or into the blood stream with involvement of

other organs such as the heart or kidneys. Involvement of the bronchi would appear to be a fairly constant finding, ranging from simple ulceration of the epithelial lining to large destructive ulceration and abscess formation causing a broncho-pulmonary fistula. The authors contend that the disease is one of spread of infection through the bronchial pathway rather than via the lymphatics or blood stream, for which there appears to be scanty support. The formation of the bullae is fully discussed; the long-standing controversy that they may be due to abscess formation or to tension cysts remains speculative, and the answer is perhaps to be found in a combination of both.

The management and treatment cover the prevention and early treatment of staphylococcal infection in the newborn and young infants, the use of corticosteroids in addition to antibiotics, and the careful management of hydration and serum chemistry.

[This is a thoughtful and stimulating paper.]

David Morris

884. Prevention of Complications of Respiratory Illnesses in Pediatric Practice: a Double-blind Study

E. H. TOWNSEND JR. and J. F. RADEBAUGH. *New England Journal of Medicine* [New Engl. J. Med.] 266, 683-689, April 5, 1962. 16 refs.

A study of the value of antimicrobial drugs in the prevention of bacterial complications in children suffering from a febrile respiratory illness of viral origin during a non-epidemic period is reported from the University of Rochester School of Medicine and Dentistry, New York. A double-blind method was used, the children being given either symptomatic treatment or one of the following antimicrobial drugs: a sulphonamide, penicillin, tetracycline, or chloramphenicol. The 781 patients included in the trial were divided into three diagnostic groups: measles, croup, or other respiratory infections. These groups were then further divided into patients in whom complications developed and those in whom no complications occurred.

It was found that the use of an antimicrobial drug did not influence the duration of the primary illness. The incidence of bacterial complications, whether or not these increased the duration of the illness, was in no way affected by the prophylactic administration of antibiotics. Such complications occurred both in patients given antimicrobial drugs and in those given symptomatic treatment without reference to past history, symptoms at onset, the results of physical examination, or the laboratory findings. The double-blind procedure was broken in 45 cases when a complication developed for which another therapeutic agent was necessary.

It is concluded that the free use of antibiotics in non-microbial respiratory infections in children is not justified.

E. H. Johnson

885. On the Treatment of Cerebral Palsy. The Outcome of 177 Patients, 74 Totally Untreated

R. S. PAINE. *Pediatrics* [Pediatrics] 29, 605-616, April, 1962. 16 refs.

From 1,821 patients with cerebral palsy, known to the Children's Hospital, Boston, Massachusetts, between 1930 and 1950, but not all admitted to its wards, 177 over 14 years old were selected who had had either well-documented intensive treatment for at least 5 years or else no treatment at all. The latter group, 74 in number, were untreated for

various reasons—for example, on medical advice (chiefly mild spastics, severely mentally retarded children, and some athetoid subjects), or because of parental disinterest or lack of facilities.

Reviewing the results, the author suggests that intensive treatment—namely, the wearing of braces, surgery, and physiotherapy of the type available at that time—was chiefly of value in patients with moderately severe spastic lesions, and results in these cases were better where treatment was started before the child was 2 years old.

Amongst the athetoid group the end-results appeared to depend on the original severity of the handicap and to be uninfluenced by treatment. Nevertheless, the author stresses the advisability of a trial of intensive physiotherapy in these cases for its psychological effect on patients and parents; he also points out that more modern methods of physiotherapy may produce better results.

Janet Q. Ballantine

886. Late Prognosis of Severe Head Injuries in Childhood

B. HJERN and I. NYLANDER. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 113-116, April, 1962. 5 refs.

This is a follow-up study, from the Kronprinsessan Lovisas Barnsjukhus, Stockholm, of 22 cases of severe head injury in children between the ages of one and 14 years. The paediatric surgery department of this hospital receives between 300 and 600 children with acute head injuries annually. In the last 10 years there have been only 2 deaths directly attributable to the head injury. The present study deals only with the seriously injured—that is, those in whom the duration of unconsciousness was 24 hours or longer. There were 23 such cases (18 boys and 5 girls) but one was lost to follow-up, the duration of which ranged from 6 months to 9½ years. Of the 22 children kept under observation, 13 have neurological or psychiatric symptoms evaluated as sequelae, 3 are completely normal, and 6 have slight symptoms attributed to causes other than the head injury. Of the 13 children with sequelae, these were neurological only in 7, psychiatric only in one, and both neurological and psychiatric in 5.

Symptoms causing severe invalidism are present in 3 of these children: one with cerebral palsy and mental retardation; one with gross personality alteration and mental retardation; one with slight cerebral palsy and so severe a personality alteration that periodically she cannot be cared for at home. In 3 children the symptoms are serious but have not led to invalidism: one girl has partially diminished hearing, psychomotor epilepsy, and slight lowering of psychological level; a boy has loss of sensation in half of the face and total deafness in one ear; another boy has facial paralysis, moderate spastic paralysis of the extremities, and slight lowering of psychological level. Slight symptoms evaluated as sequelae are present in 7 children—2 with slight paralysis of the extremities, 3 with impaired hearing, one with slight speech disturbance, and one with slight lowering of psychological level and post-traumatic neurosis. No certain correlation was found between the duration of unconsciousness and the severity of the sequelae. In several children severe symptoms present on discharge from hospital gradually improved with time; such improvement may continue for many years. The evaluation of mental retardation was difficult and the authors consider that the incidence of oligophrenia is high in accident-prone children.

Andrew M. Desmond

Public Health

887. Mass Oral (Sabin) Poliomyelitis Vaccination: Virological and Serological Surveillance in Czechoslovakia, 1958-9 and 1960

K. ŽÁČEK, E. ADAM, V. ADAMOVÁ, V. BURIAN, D. ŘEZÁČOVÁ, E. SKRIDLOVSKÁ, N. VANĚČKOVÁ, and V. VONKA. *British Medical Journal* [Brit. med. J.] 1, 1091-1098, April 21, 1962. 1 fig., 25 refs.

The authors of this paper from Charles University, Prague, summarize their experience in Czechoslovakia of oral Sabin poliomyelitis vaccine, a field trial being carried out in 1958-9, and a nation-wide campaign in 1960. In the former trial Type 1, Type-3, and Type-2 virus vaccines were given separately in that order at monthly intervals. In the nation-wide campaign two methods of administration were tried: (1) Type 1, followed a month later by Types 2 and 3 together; and (2) a single dose of trivalent vaccine. By May, 1960, 92% of all children in the age group 2 months to 14 years had been vaccinated.

In the group in the field trial receiving the three virus types separately, the total serum conversion rate was 96.3% with no significant difference between the individual types. In the group in the 1960 campaign who received Type-1 virus followed by a mixture of Type-2 and Type-3 a month later, the conversion rate was 92.7%, and the percentage response to Type-3 virus among those without antibodies to more than one type before vaccination was lower than in the field trial. The response to the trivalent vaccine was less satisfactory, only 65.3% of children having triple-positive antibodies after the vaccine. The weakest response was to Type-1 virus.

*In the field trial, vaccination of 40% of the children in an area did not affect the immunological response of non-vaccinated children. The attenuated virus did not persist in the population for more than a few months. Although 92% of children were immune to all virus types one month after the field trial this figure had fallen to 78% a year later. Revaccination 12 months later with the trivalent form resulted in 100% immunity, judged by antibody production.

In an addendum the authors state that a further nation-wide vaccination campaign was carried out in 1961. By June of that year some 90% of the child population had been revaccinated, having received Type-1 virus vaccine followed a month later by a mixture of Type-2 and Type-3. No virologically confirmed case of poliomyelitis was seen in Czechoslovakia up to December, 1961.

E. H. Johnson

888. Antibody Response in Infants to the Poliomyelitis Component of a Quadruple Vaccine

I. B. HILLARY, P. N. MEENAN, A. P. GOFFE, G. J. KNIGHT, A. D. KANAREK, and T. M. POLLOCK. *British Medical Journal* [Brit. med. J.] 1, 1098-1102, April 21, 1962. 2 figs., 10 refs.

A study of the poliomyelitis antibody levels in infants given a quadruple vaccine against diphtheria, pertussis, tetanus, and poliomyelitis is reported from University College, Dublin. One group of 24 infants received the quad-

ruple vaccine while another group of 18 were given the triple vaccine (diphtheria, pertussis, and tetanus) and poliomyelitis vaccine in different sites at the same time. A Salk-type poliomyelitis vaccine was used in both trials. The poliomyelitis antibody levels in the two groups were compared after a primary course of three injections at monthly intervals and again after a booster dose 6 months later.

Estimation of pre-vaccination antibody titres showed that in many infants, particularly those under 24 weeks of age; there were maternal poliomyelitis antibodies. These adversely affected the response to the vaccine, which, however, was about the same in both groups.

After the primary course of three injections there was a successful and equal antibody response against Type-2 and Type-3 poliomyelitis viruses in both groups, but the Type-1 antibody level was lower with the quadruple vaccine. After the booster dose, all infants gave antibody response to all types, but the levels for Type-1 were still higher in those children who received primary vaccination with the triple and poliomyelitis vaccines separately. E. H. Johnson

889. Poliomyelitis Vaccine and Triple Antigen. Efficacy Given Separately and Together

N. R. BUTLER, P. F. BENSON, B. D. R. WILSON, F. T. PERKINS, J. UNGAR, and A. J. BEALE. *Lancet* [Lancet] 1, 834-836, April 21, 1962. 4 figs., 11 refs.

The authors have compared the antibody responses in three groups of 3-month-old children, the groups having received respectively triple antigen (diphtheria, pertussis, and tetanus) and poliomyelitis vaccine simultaneously in separate arms, poliomyelitis vaccine alone, and triple antigen alone. The responses to the diphtheria, tetanus, and Type-2 and Type-3 poliomyelitis antigens were found to be satisfactory. The responses to Type-1 poliomyelitis and pertussis antigens were, however, less satisfactory. The authors consider that improvement in the potency of the Type-1 poliomyelitis virus and pertussis antigen would make possible the production of a quadruple antigen.

Franz Helmman

890. Epidemic Occurrence of Adenovirus Type 7 Infection in Helsinki. [In English]

E. JANSSON, O. WAGER, P. FORSSELL, and R. STENSTRÖM. *Annales paediatricae Fenniae* [Ann. Paediat. Fenn.] 8, 24-34, 1962. 3 figs., 18 refs.

An account is given of the clinical features of two outbreaks of respiratory infection involving 46 patients treated at the Aurora Hospital, Helsinki. The disease was encountered in the autumn of both 1959 and 1960 and affected children of school and pre-school age. Adenovirus Type 7 was isolated from specimens of faeces collected 3 to 10 days after onset in 24 cases, and in a further 22 cases the complement-fixation test showed a significant rise in antibody titre. Throat washings were also examined from a few cases, and in 4 the virus was isolated from these as well as from the stools. In most instances there was an abrupt onset, with fever of about a week's duration; this was accompanied by

cough, vomiting, and diarrhoea. Radiological evidence of pneumonia was obtained in 15 cases, the changes being said to resemble those of virus pneumonia. Conjunctivitis was found in 7 children and lymphadenitis in 4. Rigidity and pain in the neck and back gave rise to suspicion of meningeal involvement in 7 cases; in one case this was accompanied by facial paralysis and in another by a pleocytosis in the cerebrospinal fluid. •

J. E. M. Whitehead

891. **An Adenovirus Epidemic Due to Types 1 and 2.** [In English]

P. FORSSELL, H. HALONEN, R. STENSTRÖM, E. JANSSON, and O. WAGER. *Annales paediatricae Fenniae* [Ann. Paediat. Fenn.] 8, 35-44, 1962. 2 figs., 17 refs.

An outbreak of adenovirus infection in children, in whom the symptoms were predominantly gastro-intestinal and sometimes accompanied by a rash, occurred in Finland in the winter of 1960-1. This paper is concerned with the clinical features of the outbreak as seen in 50 children treated at the Aurora Hospital, Helsinki. The diagnosis was established by virological means. Adenovirus Type 2 was isolated from the faeces of 15 children, Type 1 virus from 5, and an untyped adenovirus from 4 others. Serological evidence of infection was obtained in the remaining 26 children, from whom no virus was isolated. Although most of the patients suffered from pharyngitis with coryza and cough, none showed any lymphadenitis and only 2 had conjunctivitis. Fever was present in most cases and lasted from 4 to 7 days, occasionally longer. As the fever subsided a rash appeared in 9 children; this was maculo-papular in character and was distributed on the trunk and sometimes on the face also, and was said to resemble the rash of erythema subitum. Four children complained of abdominal pain, 22 suffered from diarrhoea, and 31 from vomiting. The gastro-intestinal symptoms were of short duration, lasting 2 to 3 days in most instances.

J. E. M. Whitehead

892. **Trials of Live Influenza Vaccine in the Royal Air Force: a Report to the Medical Research Council Committee on Influenza and Other Respiratory Virus Vaccines**

J. C. McDONALD, A. J. ZUCKERMAN, A. S. BEARE, and D. A. J. TYRRELL. *British Medical Journal* [Brit. med. J.] 1, 1036-1042, April 14, 1962. 17 refs.

This report from workers at the Central Public Health Laboratory, Colindale, and the Common Cold Research Unit, Salisbury, is based on two trials of live influenza vaccine. The Russian Iksha strain of influenza A2 virus was prepared to give suspensions with titres of 10^7 per ml. and 10^6 per ml. 50% egg-infective doses, 0.5 ml. of one of these suspensions being inoculated into each nostril of volunteers. Virus isolation was made in the amniotic fluid of fertile hens' eggs. Serum was tested for neutralizing, haemagglutination-inhibition, and complement-fixing antibody.

In the first trial 64 men, some of whom had influenza antibody in their sera, were inoculated with one of the virus suspensions. Four weeks later 46 of these received a second dose. The subjects were bled at intervals, throats were swabbed for virus, and all were observed for febrile reactions. The virus was isolated from 5 (12%) of 42 men who had initial antibody and from 12 (55%) of 22 who did not. These figures, although small, are regarded as signifi-

cant. About 75% of those inoculated had a fourfold or greater rise in titre in at least one of the three serological tests employed. Those initially without neutralizing antibody and those from whom virus was recovered showed a rise in complement-fixing antibody titre. In the remainder the rise occurred in the titre of neutralizing or haemagglutination-inhibition antibody. Serological responses were greater in those given the larger dose. Three of those inoculated had fever. In 3 bedroom contacts virus was subsequently isolated from throat swabs, although they had no symptoms.

In the second trial 513 men and women received vaccine and the same number were given diluent. Only 25 had fever, which in most instances was thought to have occurred by chance. Because of the absence of influenza A infection no information on the protective effect of the vaccine could be deduced.

A. E. Wright

893. **Inactivated Influenza Vaccine in an Industrial Undertaking**

G. J. FORTUIN, G. C. SOETERS, and A. VAN BEEK. *British Medical Journal* [Brit. med. J.] 1, 1042-1045, April 14, 1962. 2 figs., 22 refs.

The efficacy of inactivated influenza vaccine was studied at the Philips Health Centre, Eindhoven, Holland, by observing sickness absence rates. A mixed vaccine was offered to 45,000 persons, of whom 11,000 were inoculated. Results were studied in 35 groups each containing vaccinated and non-vaccinated subjects.

Absence from work due to illness is normally plotted continuously in the Philips factories, and it has been found that there is a basic incidence rate (B.I.R.) upon which, in epidemics, is superimposed an extra incidence rate (E.I.R.). The B.I.R. can be calculated from previously established averages, and thus it was possible to study the E.I.R. due to an influenza epidemic occurring shortly after the vaccination programme was completed. When the E.I.R.'s for vaccinated and non-vaccinated employees were considered separately it was found that vaccination had reduced sickness absence rates by 65 to 70%.

A number of possible errors in the methods are discussed.

A. E. Wright

894. **A Milk-borne Outbreak Due to *Salmonella typhimurium***

W. H. PARRY. *Lancet* [Lancet] 1, 475-477, March 3, 1962. 17 refs.

Between July 19 and Aug. 5, 1961, an explosive outbreak of gastroenteritis occurred in Liverpool, the causative organism being *Salmonella typhimurium*, phage-type I, var. 5, which was isolated from 13 of the 16 affected patients. In addition, 5 symptomless carriers were discovered in home contacts. The only common article of food was raw tuberculin-tested milk from a herd in which one cow had recently had diarrhoea and subsequently died. If this cow was the source of infection its illness was of such a short duration that little contaminated milk could have been sold, this accounting for the small number of people affected out of the total of over 2,000 supplied. No carriers were found among the dairy staff.

The author gives details of and references to similar outbreaks occurring over the past 10 years.

A. E. Wright

Industrial Medicine

895. **Some Electroencephalographic Indices in Chronic Manganese Poisoning.** (Некоторые электроэнцефалографические показатели при хронической интоксикации марганцем)

D. A. GINZBURG. *Гигиена Труда и Профессиональные Заболевания* [Gig. Tr. prof. Zabol.] 6, 37-43, Feb., 1962. 3 figs., 20 refs.

Previous work has shown that in many patients suffering from Parkinsonism due to chronic manganese poisoning abnormalities are present in the electroencephalogram (EEG)—namely, depression of the α -rhythm and slow waves. The EEG was studied during application of rhythmic light stimulation in 42 patients exposed to manganese during their work. The patients were divided into three groups: (1) those with severe Parkinsonism, (2) those with early Parkinsonism, and (3) patients with no clinical evidence of manganese poisoning. In 9 of the 14 patients with severe Parkinsonism diffuse changes in the EEG were observed, with depression of the α -rhythm and the appearance of slow waves. The EEG was not modified by the application of the rhythmic light stimulus. The EEG in patients with mild or no clinical manifestations of manganese poisoning differed little from those of normal controls. In 6 of the 42 patients the application of the rhythmic light stimulus led to the development of photomyoclonus of the eyelids.

Basil Haigh

896. **Experimental Investigation of Tellurium as an Industrial Poison.** (Экспериментальные исследования по характеристике теллура как промышленного яда)

S. E. SANDRASKAJA. *Гигиена Труда и Профессиональные Заболевания* [Gig. Tr. prof. Zabol.] 6, 44-50, Feb., 1962. 9 refs.

The object of this investigation was to study the toxicity of tellurium (Te) and its compounds by experimental administration as aerosols, to compare the toxicity of condensation and disintegration aerosols, and to distinguish between the action of Te and TeO₂ aerosols, which are most commonly encountered in industry.

Male albino rats were exposed for 2 hours daily for 13 to 15 weeks to aerosols of known concentration. The colour index, serum protein level, liver and kidney function, and the state of the nervous system were studied, and the animals examined post mortem. The highly dispersed TeO₂ condensation aerosol was found to be the most toxic. In a concentration of 0.05 mg. per litre it depressed the rate of growth of the animals, lowered the blood haemoglobin concentration and the erythrocyte count, reduced the catalase content, disturbed the normal proportions of proteins in the serum, and acted as a thiol poison. The liver was most susceptible, undergoing fatty degeneration and depression of synthetic function. Tests of nervous function showed prolongation of chronaxie and paresis of the hind limbs and tail. A lower concentration of this aerosol caused similar, but transient and less severe, changes. Te and TeO₂ disintegration aerosols were approximately one-tenth less toxic than the condensation type. The changes produced are revers-

ible. There was no difference between the character and degree of toxic action of Te and TeO₂ disintegration aerosols. The maximum concentration of tellurium allowed should depend on the form in which it exists as a hazard.

Basil Haigh

897. **Multiple Carcinoma and Diffuse Papillomatosis of the Renal Pelves and Ureters Due to Benzidine.** (Carcinomi multipli e papillomatosi diffusa dei bacinetti renali e degli ureteri da benzidina)

E. SARTORELLI, A. GRIECO, and F. RILKE. *Medicina del lavoro* [Med. d. Lavoro] 52, 706-712, Nov., 1961 [received May, 1962]. 3 figs., 17 refs.

The authors, writing from the Clinic of Industrial Medicine of the University of Milan, first point out that extravascular tumours caused by aromatic amines, particularly benzidine, are rare. They then describe the clinical course and post-mortem findings in a man who had worked with benzidine in whom multiple carcinomata and papillomata developed.

A 60-year-old man had worked for about 19 years in a factory making azo-dyes where he was exposed to the absorption of benzidine sulphate and, to a lesser extent, benzidine base, both by inhalation and absorption through the skin. For preventive purposes cystoscopy was carried out 9 times between 1938 and 1958, with negative results, but in 1958 repeated Papanicolaou staining of the urinary sediment showed collections of cells, sometimes in masses, with evident changes of a neoplastic nature. The patient stopped work in 1959. At that time he had incipient and progressive renal insufficiency with colic and haematuria. The condition worsened and in 1961 he was admitted to the clinic in uraemic coma, from which he died 4 days later. Intravenous pyelography performed at another hospital before admission to the clinic showed left hydronephrosis and probable exclusion of the right kidney. Necropsy revealed a small right and an enlarged left kidney. Small nodules and plaques were present in both renal pelves and in the ureters, and the left ureter was dilated and thickened. No such growths were found in the bladder. Histologically, the papillomata had several layers of atypical transitional epithelium and in some places infiltration of the mucosal, muscular, and connective-tissue layers.

The authors consider that since the non-infiltrating forms of papillomata of the upper urinary passages are more frequently multiple than the infiltrating ones, the condition is more probably one of primary multiplicity than of metastases, a view which is supported by the fact that it is bilateral. They suggest that in the present case there was first a diffuse papillomatosis which later gave rise to multiple carcinomata leading to bilateral hydronephrosis and progressive renal insufficiency. Points in favour of the condition being occupational are: (1) the patient was exposed for a long time to benzidine; (2) cases of carcinomata of the renal pelves and ureters due to aromatic amines have been described in the literature; and (3) the type of tumour present was typical of that produced by such products. However, the authors cannot explain the extravascular location as compared with the more usual site in the bladder, and they agree with

Clayson's suggestion that *ortho*-hydroxyamine is converted into 3-3'-dihydroxybenzidine, which is carcinogenic, when the *para* position of the aromatic amine group is blocked by biological hydroxylation. Finally, they stress the importance of the positive Papanicolaou staining of the urinary sediment after repeated negative cystoscopy.

W. K. Dunscombe

OCCUPATIONAL DISEASES

898. Sickness Absence in Teachers

J. SIMPSON. *British Journal of Industrial Medicine* [Brit. J. Industr. Med.] 19, 110-115, April, 1962. 4 figs., 24 refs.

The records of 738 male and 1,684 female teachers employed by the Education Authority of the City of Edinburgh during the academic year September 1, 1954, to July 31, 1955, have been studied to ascertain the amount and distribution of sickness absence according to age and sex, and the findings compared with similar figures for the year 1950-51. Sickness absences were divided into two groups, those of 4 days and more, and those of 3 days and less. Absences of 4 days or more were fairly evenly distributed at all ages in both sexes, with a tendency to rise with age in the males. There was little difference between 1950-51 and 1954-55. For absences of 4 days or more the average annual duration per person for males was 2.93 days at the age of 25 and 7.62 days at the age of 60, while for females it was 8.11 days at age 20 and 8.55 days at age 60. An interesting feature was that the amount and duration of sickness absence experienced by single and married women teachers were about the same. In the case of the shorter illnesses (3 days or less) there was a tendency for this to be greater in the younger age groups in both sexes. One finding of importance was that in both male and female teachers the highest inception rates for sickness are found at the beginning of a career in teaching. In men this rate was 0.31 at age 25, falling to 0.24 at age 40, and rising again to 0.38 at age 60. In the case of women it was 0.52, 0.29, and 0.35 at ages 20, 45, and 60 years respectively.

The author suggests that man's reaction to the situation he encounters in his daily life may affect his internal processes and therefore his susceptibility to illness during adult life, and therefore that illness is influenced by his relation to the society in which he works. In this study there was some evidence that the prospect of promotion reduced the sickness absence rate, notably in teachers aged 30 to 44.

Kenneth M. A. Perry

899. Phosphorus Necrosis of the Jaw: a Present-day Study J. P. W. HUGHES, R. BARON, D. H. BUCKLAND, M. A. COOKE, J. D. CRAIG, D. P. DUFFIELD, A. W. GROSART, P. W. J. PARKES, and A. PORTER. *British Journal of Industrial Medicine* [Brit. J. Industr. Med.] 19, 83-99, April, 1962. 20 figs., 11 refs.

In this paper from a large industrial concern in England the authors review the historical aspects of "phossy jaw" (phosphorus necrosis of the jaw) and the history of phosphorus manufacture, and then describe 10 new cases. Bristowe, whose clinical description of the disease (1862) is quoted in full, suggested that phosphorus may act in one of two ways: it may affect the blood directly, the jaw disease being secondary, or the fumes may act on decayed teeth and thus predispose the adjacent jaw bone to necrosis. The

evidence in support of each of these theories is discussed. Apart from a relative lymphocytosis found in one of the 10 patients, no evidence of systemic absorption of phosphorus was demonstrable, but several examples are quoted from the literature suggesting that phossy jaw is part of a systemic process. Examples of local trauma or infection preceding the disease were not uncommon. Difficulty was experienced in diagnosing atypical cases. Redness of the mucosa of the mouth was an early sign. Necrosis, which was characterized by pain (usually worse at night), often started at the site of a "denture sore" or of delayed healing after extraction. Sequestration occurred as an acute or chronic condition. In addition to the 10 cases of classic phossy jaw, 6 cases of delayed healing without necrosis are described. Failure of the alveolar base to resorb after tooth extraction was found more frequently in phosphorus workers than in other subjects.

Biochemical investigations of 48 phosphorus workers and 28 controls showed no significant differences between the two groups in blood haemoglobin level or leucocyte count or in the radiological appearance of the hands. The plasma levels of alkaline phosphatase, inorganic phosphorus, calcium, and magnesium estimated in 5 men from each group were normal. A more detailed clinical and biochemical examination of a man who had worked with phosphorus for 4 years revealed no abnormality, other than radiological evidence (in confirmation of the clinical finding) that a sequestrum had separated.

In the authors' series the shortest time between initial exposure to phosphorus and onset of necrosis was 10 months, and the longest 18 years. While the oral flora varied from case to case, there was a "personal susceptibility to this disease". The differential diagnosis and prevention of phossy jaw are discussed. The authors allow no workman with an unhealthy mouth to be exposed to phosphorus. Those most heavily exposed are examined every 2 months. Men needing major dental treatment or showing early signs of the disease are immediately removed from the plant. The authors note that knowledge of the disease process has not increased since the time of Bristowe's description a century ago.

Terry Coates

900. Investigation of an Outbreak of Photodermatitis Confined to One Shop in a Large Factory

D. W. W. JONES. *British Journal of Industrial Medicine* [Brit. J. Industr. Med.] 19, 100-104, April, 1962. 6 figs., 4 refs.

An outbreak of photodermatitis occurring in a foundry during the last 3 months of 1960 is described, 29 of the 106 workers being affected. Only 3 of the 1,700 factory employees outside the foundry developed dermatitis.

The eruption appeared as erythema of the face, neck, dorsum of the hands, and wrists, rapidly progressing to exudation and desquamation, but clearing in 3 or 4 days in many cases. Some lesions became chronic (lasting 2 or 3 months) and were made worse by daylight, but in milder cases only erythema and burning developed. Most of the patients came to consult on Monday mornings after a week-end away from work, especially if the weather during the week-end was sunny. As this suggested that a photosensitizing agent was concerned in the aetiology the barrier cream and liquid soap used in the factory were withdrawn, but more new cases occurred. The results of patch tests with the

soap and cream, with washings from clean and from dirty overalls, with rust-preventing substances, and with oils and lubricants were negative. The fact that a high proportion of the affected subjects worked in the vicinity of the furnaces led to the analysis of possible atmospheric contaminants near the furnaces. Aromatic hydrocarbons, phenols, carbon black, and other contaminants were found in the surrounding air but gave no reaction when extracted with ether and used for patch tests. After 2 months 13 cases occurred, 2 of which were seen by a dermatologist who had noted similar cases in local skin clinics. It was then found that the soap in the foundry shower-room was used exclusively in that room. A solution of this soap was fluorescent and a 1% solution gave equivocal results on patch testing. Typical photosensitivity developed in workers outside the foundry, all of whom had used the same soap at home. The soap was withdrawn and no new cases occurred. A 0.25% dilution of a new germicide, tetrachlorosalicylanilide (TCSA) [both a photosensitizer and a contact sensitizer] had been introduced into a popular brand of soap and first sold in July, 1960. The affected men reacted to patch tests using 1% of the soap with 0.25% TCSA, but gave no reaction when the same soap without TCSA was used. The results of "dab" tests with 1% TCSA on the cheek were positive. Further cases were noticed outside the factory. The soap manufacturers had withdrawn the product just before the outbreak started.

Terry Coates

901. Vitiligo-like Dermatoses in Workers at Phenol-Formaldehyde Resin Works. (О витилигоподобных дерматозах у рабочих производства фенол-формальдегидных смол)

N. N. SUMAKOV, G. P. BABANOV, and A. G. SMIRNOV: *Вестник Дерматологии и Венерологии* [Vestn. Derm. Vener.] 36; 3-8, April, 1962. 5 figs., 11 refs.

Vitiligo-like patches appeared on the bodies of 23 of 52 workers engaged in the production of synthetic resins. The condition, which was chronic, was thought to be due to the inhalation of phenol and formaldehyde fumes and of resin dust in concentrations exceeding the permissible maximum. The periods during which these substances were inhaled varied from one year to 9 years. The dermatoses were symmetrical in 21 of the 23 patients, the areas affected being chiefly the axillae, elbows, wrists, and ankles. The patients also had systemic symptoms and signs, prominent being headache, lassitude, thirst, and excessive sweating.

Subcutaneous injections of phenol were found to produce greying of black hair in rabbits. Histological examination of these animals showed pathological changes in the internal organs, endocrine glands, and intervertebral ganglia. The authors consider these changes to be due to the action of phenol.

N. Hopewell

902. The Study of the Bronchial Tree in Coal-miners' Pneumoconiosis. (К изучению «бронхиального дерева» при пневмокониозе шахтеров)

L. BRUKNER and I. ROSMAY: *Гигиена Труда и Профессиональные Заболевания* [Gig. Tr. prof. Zabol.] 6, 32-37, Feb., 1962. 6 figs.

In this study of the bronchial tree in pneumoconiosis, 150 coal-miners were divided into 10 groups according to age, duration of exposure to dust, and degree of pneumoconiosis. Attention was paid to history, clinical findings, the results

of chest radiography, and laboratory tests. Bronchography was carried out on each miner, and the findings were compared with the other data. The investigation showed that in pneumoconiosis in middle-aged miners engaged in this occupation for 15 years, functional and morphological changes develop in the bronchi, even in the absence of definite radiological signs of pneumoconiosis. The degree of the bronchial changes depends on the degree of development of the pneumoconiosis and not on the age of the miner or on how long he has been at work. The clinical features do not correspond to the degree of severity of the bronchial changes. The latter in typical nodular pneumoconiosis can be distinguished qualitatively and quantitatively from those in progressive massive fibrosis.

The authors conclude that bronchography is indicated when the results of clinical examination and of function tests do not correlate with the patient's subjective complaints, or when marked signs are found on auscultation, especially if these are unilateral. Bronchiectasis is a more frequent finding in coal-miners' pneumoconiosis than has hitherto been considered to be the case.

Basil Haigh

903. The P Wave and Respiratory Function in Silicosis. (Comportamento dell'onda P e della funzionalità respiratoria nei silicotici)

T. Sessa and A. SILVESTRONI: *Folia medica* [Folia med. (Napoli)] 45, 105-128, Feb. [received June], 1962. 4 figs., 11 refs.

The authors, working at the Institute of Industrial Medicine of the University of Naples, studied the possible correlation between the P wave of the electrocardiogram (ECG) and respiratory function in 100 patients with silicosis. The elements of the P wave considered were voltage, duration, morphology, and electrical axis, while respiratory function was estimated according to the vital capacity (V.C.), the maximal ventilation per minute, Tiffeneau's index, and the index of emphysema. The ages of the patients ranged from 30 to 66 (average 50) and of the healthy controls from 20 to 55 (average 36) [the two groups were thus not comparable]. The degree of silicosis was classified (modified Geneva) as follows: linear markings, 11 cases; micronodular Stage I, 33, Stage II, 16, Stage III, 8 cases; macronodular Stage I, 7, Stage II, 14, Stage III, 7 cases; and confluent 4 cases. Diffuse bronchitis was present in 21 patients, emphysema in 16, pulmonary tuberculosis in 9, and "cardiopathy" [not further defined] in 3.

In the silicotic patients the ECG showed right axis deviation in 54% and the average voltage was greatly increased in 31%, while a number showed a diphasic P wave especially in the right precordial leads. In relation to respiratory function the voltage was notably raised in those with lower V.C. (especially below 2.5 litres). The authors stress the very close correlation between the behaviour of the atrial component of the ECG and the V.C.; they consider that in silicosis the change in the P wave and its components is proportional to the deficiency in respiratory function, but that this appears to be conditioned by the concomitant bronchitis and especially by emphysema; hypoxia is another factor in determining increase in voltage. They conclude that in silicosis modifications of the various elements of the P wave depend to a large extent on the respiratory deficit and are therefore important indirect signs of the gravity of the disease.

W. K. Dunscombe

Anaesthetics

904. **Steroid and Antihistaminic Therapy for Post Intubation Subglottic Edema in Infants and Children**
M. V. DEMING and S. R. OECH. *Anesthesiology* [Anesthesiology] 22, 933-936, Nov.-Dec., 1961. 3 refs.

This paper from the University of Pennsylvania, Philadelphia, describes a method of treating post-intubation subglottic oedema in children. The mildest form of this condition, which the authors regard as the major complication of endotracheal anaesthesia, is evidenced by hoarseness or croupy cough lasting for several hours. In the more severe cases there are, in addition, suprasternal and intercostal retraction, crowing inspiration, restlessness, sweating, anxiety, and cyanosis. Complete obstruction, if it occurs, can be relieved only by tracheostomy. There are two possible causes: (1) mechanical injury from traumatic intubation, and (2) infection. The former may result from the use of too large or too small a tube, and the latter from external contamination or from recent upper respiratory-tract infection. The first signs appear within 3 hours, and treatment should be started immediately if tracheostomy is to be avoided. The measures recommended are a high oxygen concentration and high humidity of the inspired air, control of body temperature at slightly below the normal, and an adequate parenteral fluid intake. Such measures may be sufficient, but if restlessness due to hypoxia is present, sedation with intravenous diphenhydramine chloride is suggested, in a dosage of 0.25 mg. to 0.5 mg. per lb. (0.55 mg. to 1.10 mg. per kg.) of body weight. Adrenocorticosteroids have also proved valuable, the most rapid response being obtained with dexamethasone-21-phosphate; a single dose of 4 mg. for infants under one year and of 8 mg. for older children is advised. A further dose is seldom needed. Improvement is noted 20 to 40 minutes after administration of diphenhydramine and dexamethasone.

Raymond Vale

905. **The Anesthetic Hazards in Patients on Antihypertensive Therapy**
D. L. CRANDELL. *Journal of the American Medical Association* [J. Amer. med. Ass.] 179, 495-500, Feb. 17, 1962. 5 figs., 25 refs.

This paper from the Bowman Gray School of Medicine of Wake Forest College and the North Carolina Baptist Hospital, Winston-Salem, draws attention to the hazards of anaesthesia in patients who have been receiving antihypertensive drugs. The modes of action of these drugs and the ways in which they affect the normal action of the sympathetic nervous system are reviewed. The importance of adrenaline and noradrenaline in maintaining circulatory homeostasis during anaesthesia is stressed. While the duration of action of most antihypertensive drugs is short, greater care has to be exercised with the thiazide derivatives, the rauwolfia compounds, and guanethidine ("ismelin") than with the others, because of both the mode and the duration of their action. The thiazide derivatives have been found experimentally to cause a diminished pressor response to noradrenaline. This is thought to be due to

changes in sodium and potassium concentration in the peripheral vascular wall and in the serum, changes which in themselves are associated with other anaesthetic hazards. When guanethidine has been used, inactivation of the peripheral sympathetic nervous system may persist for 5 to 7 days after its withdrawal. Reserpine depletes the catechol amine stores both centrally from the hypothalamic centres and peripherally from the postganglionic sympathetic nerve endings, and these stores take from 10 to 14 days to be replenished. Since several of the antihypertensive drugs cause an increase in cardiac vagal tone, adequate atropinization is essential before patients who have been taking them are anaesthetized. The author describes the ephedrine response test which, depending on the release of adrenaline and noradrenaline, evaluates the haemodynamic status of these patients. If, after intravenous administration of 15 mg. of ephedrine, the blood pressure does not rise by at least 20 mm. Hg and the pulse rate by 10 beats per minute, then general, spinal, and epidural anaesthesia are contraindicated. The anaesthetic management of various circumstances in which these drugs are used is discussed. Special care is necessary in employing controlled respiration in patients who have had antihypertensive drugs. The risk of hypoglycaemia is increased by the administration of drugs which block the sympathetic nervous system.

Raymond Vale

906. **"Penthrane": a Clinical Evaluation in 50 Cases**
M. W. CAMPBELL, A. P. HVOLBOLL, and V. L. BRECHNER. *Anesthesia and Analgesia; Current Researches* [Anesth. Analg. Curr. Res.] 41, 134-139, March-April, 1962. 3 figs., 3 refs.

A review of the clinical experience with "penthrane" (methoxyflurane) in 50 patients is presented. Penthrane has many features which are similar to ether plus the hypotensive properties of halothane. It is a potent, nonexplosive agent which can produce any degree of relaxation. It is difficult to vaporize in any vaporizer. It is compatible with all drugs tested thus far. Induction and emergence are generally smooth, but moderately long. There is a moderate incidence of nausea and vomiting. There is a prolonged somnolent state with decreased cough activity after long administration. There is no increase in bleeding at the operative site.

Administration is relatively easy, but the blood pressure must be monitored closely for hypotension. The eye signs, respiratory effort, and compliance do not afford a good index of depth of anaesthesia. No special vaporizer is required. The usage rate is about 4 or 5 c.c. per hour. A wandering pacemaker may be seen on electrocardiogram without a break in the cardiac rhythmicity. It has not been used in obstetrics.—[Authors' summary.]

907. **Transmural Central Venous Pressure during Intermittent Positive Pressure Respiration**
W. E. WATSON, A. C. SMITH, and J. M. K. SPALDING. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 278-286, May, 1962. 8 figs., 20 refs.

Radiology

RADIODIAGNOSIS

908. Clinical Trial of Biloptin in Oral Cholecystangiography

J. P. MURRAY. *British Journal of Radiology* [Brit. J. Radiol.] 35, 278-281, April, 1962. 5 refs.

A trial of four oral media for cholecystangiography is reported from the Regional General Hospital, Limerick, Ireland. The media were "biloptin" (sodium ipodate), "solu-biloptin" (calcium ipodate), iopanoic acid, and phenobutiodil, and the doses in each case were fractionated, 3 g. being given in the evening before examination and 3 g. on the morning of the examination. A group of 157 patients received biloptin on both occasions, 41 received biloptin in the evening and solu-biloptin in the morning, while 90 had iopanoic acid and 26 had phenobutiodil on both occasions.

Side-effects, especially nausea and vomiting, were more frequent and severe with phenobutiodil than with the other media. The total incidence of side-effects with biloptin was roughly the same as that with iopanoic acid, but the former tended chiefly to cause nausea and the latter diarrhoea. In opacification of the common bile duct before a fatty meal solu-biloptin did not differ markedly from biloptin; the proportion of cases in which the duct was seen was disappointingly small, well under 50%, and seemed lower than other workers have reported.

The author concludes that biloptin is a safe and reliable medium for routine cholecystography for the display of gall-stones and other gall-bladder conditions, but in demonstrating the duct system it is less efficacious than intravenous "biligrafin" (iodipamide methylglucamine), "for which it cannot be considered a substitute". A. M. Rackow

909. "Solu-biloptin": a Trial of "3-Hour" Cholecystography

A. W. ROBINSON. *British Journal of Radiology* [Brit. J. Radiol.] 35, 282-284, April, 1962. 28 refs.

In this investigation reported from St. Chad's and Dudley Road Hospitals, Birmingham, 100 patients were given 6 g. of "solu-biloptin" (calcium ipodate) and cholecystograms were taken 3 hours later, the object being to assess the value of the 3-hour technique in the diagnosis of gall-bladder disease. In all cases in which there was no gall-bladder shadow or only a faint one a 12-hour cholecystogram was taken after a further 6 g. of the medium had been given.

There was satisfactory visualization of the gall-bladder at 3 hours in 57 cases. In 38 of the 43 cases of faint or absent shadows the examination was repeated; of 25 in which no shadow had been seen at 3 hours, the repeat examination revealed a normal gall-bladder shadow in 8; of 13 in which the shadow had been weak, repeat examination after 12 hours revealed a stronger shadow. It is pointed out that "in no case of non-opacification of the gall-bladder in which the common bile duct was seen did the repeat cholecystogram reveal a normal gall-bladder". There were very few reactions to the drug.

The author concludes that the number of cases in which a repeat 12-hour examination was required for accurate assessment makes the 3-hour technique unreliable for routine use; nevertheless "a fair proportion of gall-bladders are adequately opacified at 3 hours and... the method may conceivably be of diagnostic value in the occasional acute abdominal case". A. M. Rackow

910. The Use of Silicone Foam for Examining the Human Sigmoid Colon

G. B. COOK and A. R. MARGULIS. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 633-643, April, 1962. 11 figs., 2 refs.

A new method of examination of the sigmoid colon is described in this paper from Washington University School of Medicine, St. Louis, Missouri. The basis of the method is the use of a radio-opaque enema which rapidly solidifies in the sigmoid into a silicone foam-rubber mould. [The original article should be consulted for further details.] The mould assumes the contour of the bowel and gives an accurate imprint of its mucosa. Indentations in the mould may show the presence of lesions; suspicious areas can be irrigated with Ringer's fluid and the diagnosis established by cytological methods. The procedure is intended for use in the small number of cases in which overlapping coils make other methods of examination unsatisfactory. The present paper includes a preliminary report in 80 selected cases (including 16 of malignant neoplasms and 13 of polyps); the authors do not, however, claim that any new or unsuspected disease condition was found. Expulsion of the mould caused little difficulty; 47 patients expelled it painlessly within 15 minutes and 29 within 36 hours. Only 6 were unable to expel it spontaneously, 4 becoming anxious and requesting removal within 24 hours. The polymer forms a soft foam so that manual removal is simple; if the mould is broken the fragments are readily reassembled. Of the 80 patients, 50 were given neostigmine. The main value of the method seems to be as an aid to cytology. Denys Jennings

911. The Diagnosis and Treatment of Dilatation of the Colon in Severe Ulcerative Colitis: a Diagnostic Roentgen Sign

M. SIMON, J. H. SHAPIRO, J. G. PARKER, C. J. SCHEIN, and B. WEINGARTEN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 655-669, April, 1962. 6 figs., 14 refs.

The purpose of this paper is to emphasize the importance of routine straight radiographs of the abdomen in patients with ulcerative colitis so that the presence of toxic dilatation can be recognized before it becomes obvious clinically. Since 1951 a total of 45 cases of acute toxic ulcerative colitis have been reported in the literature, with 13 deaths. The present authors add 7 further cases seen at Montefiore Hospital, New York, with 4 immediate deaths and one late death. The serum potassium level was normal in all the fatal cases. The dilatation may appear at any age (the ages

of the patients in this series ranged from 14 to 61 years), and is not related to the duration of the disease (10 months to 25 years). Clinical diagnosis is based on abdominal distension and tenderness with "toxicity". The permeability of the colon wall is increased, its tone lessens, and there is a *durchwanderung* peritonitis. A barium enema is unnecessary and contraindicated because of the risk of perforation. Straight radiographs, especially with a horizontal beam and the patient positioned to show fluid levels, are adequate. Routine serial radiographs showing progressive dilatation are particularly valuable because the clinical signs and symptoms may be delayed or be deceptive. *Denys Jennings*

912. Diffuse Lymphomatous Disease of the Colon: Its Roentgen Appearance

R. POCHACZEWSKY and R. S. SHERMAN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 670-684, April, 1962. 11 figs., bibliography.

A careful review of the literature [no German or Russian references are given] revealed 45 reported cases of diffuse involvement of the colon by malignant lymphoma (reticulum-cell sarcoma in 2, lymphosarcoma in 35, chronic lymphatic leukaemia in 5, and Brill-Symmers disease in 3). From the Memorial Center for Cancer and Allied Diseases, New York, 6 further cases are reported, 5 of which were diagnosed in the period 1955-60. Barium-enema examination in these cases revealed a good response to radiotherapy; no necropsy findings were available. The expectation of life from the time of diagnosis of involvement of the colon was under 2 years. [The details of each case are not tabulated and it is not clear how far involvement of the colon contributed to the patient's discomfort.] The radiological differential diagnosis is from familial polyposis, ulcerative or amoebic colitis, and, possibly, from some protein-losing enteropathies. *Denys Jennings*

RADIOTHERAPY

913. Telecobalt Therapy of Inoperable Gastric Carcinoma. (La telecobaltoterapia del carcinoma gastrico inoperabile)

G. PISANI and U. NUVOLONE. *Radiobiologia, radioterapia e fisica medica* [Radiobiol. Radioter. Fis. med.] 17, 21-29, Jan.-Feb. [received July], 1962. 11 refs.

The authors, working at the Ospedale Maggiore, Novara, Italy, used telecobalt therapy in 88 cases of gastric cancer between March, 1956, and December, 1960. In most of the cases the condition was advanced and in 28 it had recurred after operation. Great importance was attached to medical treatment before and during radiation therapy, especially to control of electrolyte balance by intravenous administration of salts and glucose; vitamin B and cortisone were also considered to have an important place in management. The technique most frequently used was two opposed fields, an anterior and a posterior, or two oblique fields of different dimensions (120 to 180 cm.²). In the most advanced cases only, a single anterior field with a grid, 15×15 cm., was used. Daily tumour doses of 150 to 200 rads were given, and the total tumour dosage varied from 2,500 to 6,000 rads. The best results were found at a total dosage of 4,000 to 5,000 rads in 3 to 5 weeks. Total dosage of less than 3,000 to 3,500 rads was found to be of little value, and of over

5,000 rads to be harmful. In 14 cases only was it found impossible to exceed 3,000 rads. In 52 patients there was no clinical disturbance from treatment. In a high proportion of the cases the tumours regressed and the survival time improved, 32 patients surviving for over 2 years and 6 for over 3 years. There was improvement in general condition and ability to eat, and pain and stenosis were relieved. Only 11 patients (12.5%) did not benefit. The results were better in the patients with the proliferative than in those with the infiltrative type of growth. Judged from the standpoint of palliation alone, apart from survival time, the treatment was considered to have been worth while. *J. Walter*

914. Clinical and Statistical Features of the X-ray Treatment of Inoperable Carcinoma of the Lung. (Considerazioni clinico-statistiche sul trattamento radiologico del carcinoma bronco-polmonare inoperabile)

S. GAVALÀ. *Minerva medica* [Minerva med.] 53, 1180-1184, April 18, 1962. 2 figs., 23 refs.

Radiotherapy is essentially a means of palliation and does not rival surgery as a curative method. It can relieve secondary changes such as bronchial stenosis. This report from the University of Bologna is based on 46 cases of inoperable carcinoma of the lung, treated by various techniques and doses of x rays. The histological type did not appear to be an important factor in determining survival. It is pointed out that the best results are to be expected in cases which are technically operable, but otherwise unsuitable for surgery. In these cases (16) the mean survival time was 7.5 months, compared with 2.2 to 5 months in the others. Multiple small fixed fields are considered the best technique, as compared with pendulum therapy or large fields. Total skin doses up to 6,000 r. gave a mean survival time of 3.8 months (3 cases); higher doses up to 18,000 r. gave 5.1 to 5.5 months [tumour doses are not given], with little difference throughout the range. Comparison with other published figures shows wide differences in the results and in the effects of variation of dosage. *J. Walter*

915. Contribution to the Study of X-ray Treatment in Cutaneous Leishmaniasis. (Contributo allo studio del trattamento roentgenterapico nella leishmaniosi cutanea)

A. C. PRATESI and G. MARIOTTI. *Radiobiologia, radioterapia e fisica medica* [Radiobiol. Radioter. Fis. med.] 16, 334-348, 1962. 4 figs., 32 refs.

After surveying the pathological and clinical aspects of cutaneous leishmaniasis, the authors describe 26 cases treated by short-distance x rays (which they regard as the treatment of choice) at the Institute of Radiology of the University of Pavia and at the Civil Hospital, Pesaro, Italy. The basic course consisted of 3 doses of 500 r., each given at intervals of a week. Most of the lesions were rapidly disappearing at the end of the course, and healing was complete a little over 2 months from the start. If progress was unsatisfactory the course was repeated after an interval of at least a month; in some cases a single additional dose sufficed. Complete success was achieved in all except 2 cases which had previously been treated by other means. Radiation does not act on the protozoon itself (which is radioresistant) but probably on the reticulo-endothelial cells, perhaps through breakdown products of radiosensitive cells assisted by capillary dilatation and influx of lymphocytes and eosinophils. *J. Walter*

ABSTRACTS OF WORLD MEDICINE

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Pathology

916. Combined Deficiency of Factor V and Factor VIII (Antihæmophilic Globulin): a Report of Three Cases

J. H. JONES, C. R. RIZZA, R. M. HARDISTY, K. M. DORMANDY, and J. C. MACPHERSON. *British Journal of Haematology* [Brit. J. Haemat.] 8, 120-128, April, 1962. 6 refs.

In this paper are described 3 cases of double deficiency of Factor V and of antihæmophilic globulin (Factor VIII). The first 2 patients were sisters, aged 34 and 41 respectively, and the third (a girl of 11) was not related. There was no consanguinity between the parents of the first 2 patients, but the parents of the third patient were first cousins.

The important laboratory findings were a significant prolongation of the one-stage prothrombin time (12.5 to 15.0 seconds control plasma; 21.4 to 30 seconds patients' plasma), and a very slight prolongation of the whole-blood coagulation time. There was an abnormality in the thromboplastin generation test on the adsorbed plasma side of the system, and the Factor VIII assay was from 10 to 20%. The clinical severity of the hæmorrhagic state was remarkably slight in the light of the results of the assays on Factors V and VIII.

The effects on the one-stage prothrombin time and on the assays of Factors V and VIII following plasma transfusions are described.

A. S. Douglas

917. The Ammonium Chloride Urinary Acidification Test as a Complement to the Study of Renal Function. (Le test d'acidification urinaire au chlorure d'ammonium, complément à l'étude des fonctions rénales)

G. GREDER and F. M. GUTTMAN. *Helvetica medica acta* [Helv. med. Acta] 29, 1-37, April, 1962. 17 figs., bibliography.

This paper, from the University of Geneva, describes a test for assessing the function of the distal renal tubules. The basis of the test, which was described by Wrong and Davies (*Quart. J. Med.*, 1959, 28, 259; *Abstr. Wld Med.*, 1959, 26, 296), is that in a normal subject the excretion of hydrogen ions is more than doubled after the ingestion of one dose (0.1 g. per kg. body weight) of ammonium chloride. The urine is collected at suitable intervals after administration of the dose, and analysed for pH, titratable acidity, ammonium, bicarbonates, chlorine, sodium, and potassium. The urinary excretion of these ions is expressed in micro-equivalents excreted per minute, from which the total spared bases are calculated.

The test was carried out on 68 subjects, of whom 10 were in normal health, 25 had "glomerular syndromes" (acute or subacute glomerulonephritis in 4, nephrotic syndrome in 5, chronic glomerulonephritis in 9, and malignant hypertension in 7), 26 had pyelonephritis and other types of interstitial nephritis, and 7 had renal stone and hypercalciuria. The following mean changes were found in the urine of

the normal subjects: a fall of pH to 4.87; a rise in titratable acid to 53.2 μ Eq. per minute; a rise in ammonium to 69.3 μ Eq. per minute; almost complete disappearance of bicarbonates; a rise in total excretion of hydrogen ions (titratable acid plus ammonium minus bicarbonate) from 45 to 116 μ Eq. per minute. Thus, the urinary changes normally observed with the ammonium chloride test are a fall in pH, increase in titratable acid, increase in ammonium, fall in bicarbonate, and increase in total spared bases.

Of the 25 cases of glomerular syndrome, 5 were mild and in them the results, at least as regards hydrogen-ion excretion, were very similar to normal. In 5 more severe cases the pH fell to 4.99 but the hydrogen excretion was only 48 μ Eq. per minute. In 8 very severe cases the pH fell to 4.93 but the hydrogen excretion was only 42 μ Eq. per minute. In the 7 cases of malignant hypertension the pH was never lower than slightly below 6 and the maximum hydrogen excretion never higher than 36.5 μ Eq. per minute. Of the 26 cases of pyelonephritis and interstitial nephritis the most instructive were 5 patients in whom the results of renal function tests were normal and in whom the pH fell normally (to 5.09), but in whom the hydrogen excretion rose to only 59 μ Eq. per minute. This illustrates well the specificity of the ammonium chloride test. In the 7 cases with disorders of calcium metabolism resulting in renal calculi and hypercalciuria the results were variable. In general, there was persistently high excretion of bicarbonate, inadequate fall in pH, and inadequate excretion of hydrogen (maximum about 60 μ Eq. per minute). [The figures given above are the mean for the respective groups of cases.]

Variations in urinary pH alone do not express adequately the results of an acidification test. Only by measurement of the total hydrogen excretion can the function of the distal tubules be assessed. The test is particularly useful in cases in which the kidney can excrete hydrogen adequately in normal conditions, but cannot deal with an extra load. It is an important complement of the concentration test, for it may permit the early detection of renal disease in cases in which the usual function tests give normal results. In generalized renal failure, on the other hand, it can do no more than confirm the results obtained with other, simpler tests. In cases of advanced acidosis it may be dangerous.

G. Clayton

918. Leucine Prolongation of Tolbutamide-Induced Hypoglycemia

T. S. DANOWSKI, J. V. BONESSI, W. R. BALASH, and C. MOSES. *Metabolism: Clinical and Experimental* [Metabolism] 11, 556-561, June, 1962. 3 figs., 24 refs.

Administration of leucine has no effect on the blood glucose level in healthy subjects but may lower the level in certain patients with idiopathic hypoglycaemia, those with

an insulin-secreting adenoma, and in patients treated with chlorpropamide. In this study reported from the University of Pittsburgh School of Medicine, Pennsylvania, leucine was given by mouth in a dosage of 0.15 g. per kg. body weight to healthy fasting male prisoners. It was found to prolong the lowering effect on the blood sugar level of tolbutamide but not that of insulin. The fall in the serum phosphate content which followed both tolbutamide and insulin administration was increased by leucine, which, however, did not lower the serum potassium level except in conjunction with tolbutamide. These results are interpreted as indicating a continuing effect of leucine on insulin secretion once this process has been started by tolbutamide.

H. Lehmann

919. Effect of ACTH, Hydrocortisone, and Glucagon on Plasma Nonesterified Fatty Acid Concentration (NEFA) in Normal Subjects and in Patients with Liver Disease. D. A. DREILING, E. L. BIERMAN, A. F. DEBONS, P. ELSBACH, and I. L. SCHWARTZ. *Metabolism: Clinical and Experimental [Metabolism]* 11, 572-578, June, 1962. 5 figs., 14 refs.

The effect of certain hormones on the plasma concentration of non-esterified fatty acids in patients with acute viral hepatitis and viral hepatitis complicating cirrhosis was studied at Mount Sinai Hospital, New York. Whereas in healthy subjects injection of corticotrophin (ACTH) or hydrocortisone caused a fall in the plasma level of non-esterified fatty acids, no such effect could be seen in the patients with liver disease. Glucagon, on the other hand, produced a fall in this level both in patients and healthy controls. It was notable that the patients responded to glucagon even if this substance failed to elicit a rise in the blood sugar level. The authors postulate that ACTH and hydrocortisone act on carbohydrate and fat metabolism in the liver and that glucagon may have a direct effect on the metabolism of adipose tissue which is quite independent of its effect on liver glycogen.

H. Lehmann

920. New Method for the Determination of Whole-blood Iron and Hemoglobin

H. V. CONNERTY and A. R. BRIGGS. *Clinical Chemistry [Clin. Chem.]* 8, 151-157, April, 1962. 9 refs.

The authors describe a new method for determining the iron content of whole blood, developed by them at the Veterans Administration Hospital, Wilmington, Delaware. This is based on the assumption that sodium hypochlorite solution would free the iron from the haemoglobin molecule more efficiently and more rapidly than either the cold concentrated sulphuric acid used in the Wong method or the boiling acid mixtures used in the digestion methods. Sodium hypochlorite and hypochlorous acid were also powerful oxidizing agents which converted the iron to the ferric state and thus functioned admirably to favour thiocyanate colorimetry. Their method employs only 3 reagents in addition to the standard, and complete analysis can be performed in less than 15 minutes. The hypochlorite solution used was a commercially available laundry bleaching fluid free from iron and containing 5.4% sodium hypochlorite.

The procedure is as follows. To 2 ml. of a filtered dilution of an oxalated blood sample in a 50-ml. flask is added 5 ml. of the sodium hypochlorite solution. After mixing, 2 minutes is allowed for decolorization of the haemoglobin to

occur. Then about 25 ml. of distilled water is added, followed by 10 ml. of 50% v/v sulphuric acid. A scanty flocculent precipitate forms. The contents of the flask are then mixed thoroughly and water is added almost to the 50-ml. mark. Foam is dispelled with one drop of caprylic alcohol and the flask then filled exactly to the mark. The solution is mixed well and filtered. To 10 ml. of the filtrate 2.5 ml. of 10% solution of ammonium thiocyanate is added and the two mixed together. The absorbance is measured at 480 mμ against a blank.

The accuracy of the method was established by recovery experiments, which showed that a linear relationship existed between the volume of a given haemoglobin solution analysed and the total amount of iron released, as well as by the demonstration that a constant fixed ratio existed between haemoglobin iron and haemoglobin (as cyanmethaemoglobin). The new method is said to be easier to perform than the procedure of Wong.

G. Clayton

921. Extraneural Lesions Associated with Neonatal Hyperbilirubinemia and Kernicterus

J. BERNSTEIN and B. H. LANDING. *American Journal of Pathology [Amer. J. Path.]* 40, 371-391, April, 1962. 10 figs., 21 refs.

In this paper from the Children's Hospitals of Michigan and of Cincinnati the authors compare the incidence of necrotic lesions in extraneural tissues in a group of 69 newborn infants with kernicterus and in a control group of 50 jaundiced newborn infants without kernicterus. The first group were consecutive necropsy cases at the Children's Hospital of Michigan, infants with known infections being excluded. Of the 69 infants, 44 were premature, 12 of whom had haemolytic disease, and 25 were full-term, 23 of whom had haemolytic disease. The control group consisted of 30 premature infants, 5 with haemolytic disease, and 20 full-term infants, 8 with haemolytic disease. The incidence of necrosis was assessed on an arbitrary scale, by examination of sections stained with haematoxylin-eosin, tissues in which a recognizable primary pathology was present being excluded. Frozen sections of organs taken from the 10 most recent cases of kernicterus were also examined for bilirubin crystals. The organs compared were spleen, stomach, intestines, pancreas, renal cortex and medulla, adrenal, gonad, mucous and salivary glands, and bone marrow. In the control group, although slight necrosis was frequently seen, necrosis of moderate degree was uncommon, ranging from zero to 8.5% in different organs. In the kernicterus group, however, 75% of the cases had lesions of moderate, or greater, severity, the spleen and gastro-intestinal tract being the organs most commonly affected. The lesions were necrobiotic in nature, with a variable degree of leucocytic infiltration, and were of focal distribution. The authors describe in detail the appearances in different organs, and tabulate the frequency of multiple lesions. The correlation of necrosis with bilirubin deposits as seen in frozen sections was not very satisfactory owing to prolonged fixation, but the renal medulla and adrenal showed the most marked deposits.

The authors conclude, that the differences between the cases with kernicterus and those without were sufficient to suggest that bilirubin was the toxic agent. They discuss the pathogenesis of the lesions and their possible clinical significance.

E. G. Hall

Microbiology and Parasitology

VIRUSES

922. **Excretion of Vacuolating SV-40 Virus (Papova Virus Group) after Ingestion as a Contaminant of Oral Polio-vaccine**

J. L. MMLNICK and S. STINEBAUGH. *Proceedings of the Society for Experimental Biology and Medicine [Proc. Soc. exp. Biol. (N.Y.)]* 109, 965-968, April [received June], 1962. 1 fig., 13 refs.

The vacuolating virus SV40 occurs frequently as a latent contaminant of cultures of rhesus monkey kidney tissue as used for the production of poliomyelitis virus vaccine. Until it became possible to detect the presence of the virus by subculture to cultures of kidney tissue of the African green monkey, in which it produced a cytopathic effect, it was an adventitious constituent of many batches of killed and live poliomyelitis virus vaccines. This paper from Baylor University College of Medicine, Houston, Texas, reports studies of the faecal excretion of the virus by children who, in earlier trials of live poliomyelitis virus vaccine, had inadvertently received live SV40 virus. Of 47 children aged 3 to 6 months given 100 to 1,000 plaque-forming units by mouth, 9 were found to excrete vacuolating virus from the third week onwards after vaccination. Children who became infected in this way excreted less of the poliomyelitis virus and for shorter periods than those who remained free from infection with SV40, presumably because of viral interference. Two other groups of newborn infants were infected with a 10- to 100-fold larger dose of SV40 virus. In one group no virus excretion was observed, possibly because the specimens were collected not later than the second week after vaccination; in the other group virus was excreted up to 5 weeks afterwards. The authors point out that no illness has been attributable to this virus among the many hundreds of thousands of children who have received the virus by injection or by mouth.

[The interest in this virus as a contaminant of vaccines for human use has been heightened by the demonstration of its capacity to produce tumours in newborn hamsters.]

J. E. M. Whitehead

923. **A Lipogenic Toxin Released Through the Interaction of a New Cytopathic Agent (Lipovirus) and Cultured Human Cells**

R. S. CHANG, R. P. GEYER, and S. B. ANDRUS. *Journal of Experimental Medicine [J. exp. Med.]* 115, 959-966, May 1, 1962. 2 figs., 9 refs.

Workers at the Harvard School of Public Health, Boston, have isolated an apparently new virus from the blood of patients in the acute phase of infective hepatitis. Since the surface coating of the agent is rich in lipids, it is tentatively referred to as lipovirus. In human cell cultures infected with this lipovirus is found a toxic factor, which is dissociable from the infective particles. It induces sudanophilia of human and mouse cells, an increase in the total fatty acid content, and a change in the major constituent fatty acids. No similar toxin is demonstrable in cultures infected by

vaccinia, herpes simplex, adeno 3, polyoma, poliomyelitis Types 1 and 2, Coxsackie B1, para-influenza A, and Rous sarcoma viruses.

Preliminary characterization of this toxin indicates that it is resistant to tryptic digestion, is not dialysable, and is not neutralized by human gamma globulin. It is inactivated at 58° C. for 30 minutes, but is stable at 37°, 4°, and -60° C.

The authors speculate whether in the appropriate *in vivo* situation, infection with or survival of the lipovirus might be accompanied by slow, continued release of the toxin into the circulatory system with resultant fatty changes at susceptible sites. To substantiate this hypothesis, it would be necessary to establish replication of the lipovirus in animals, to demonstrate its lipogenic activity *in vivo*, and to achieve repeated isolations from clinical material.

D. Geraint James

924. **A Study of the Mechanisms of DNA and Thymine Degradation in Cultured Human Cells Infected with a Lipovirus**

R. S. CHANG and H. LIEPINS. *Journal of Experimental Medicine [J. exp. Med.]* 115, 967-976, May 1, 1962. 15 refs.

A lipovirus has been isolated from human blood and transmitted in cell cultures at the Harvard School of Public Health, Boston. This report presents data indicating "that the degradation of thymine-2-C¹⁴ with formation of C¹⁴O₂ occurs only in cultures infected with the lipovirus... consistent failure to detect any conversion of thymine to CO₂ in cultured human 'liver', embryonic, amnion, mouse embryonic, and chick embryonic cells, either alive, killed by physical and chemical agents, or infected by a variety of viral agents, suggests the possibility that the genetic information for the synthesis of one or more enzymes necessary for these catabolic reactions is absent in these cultured cells. The consistent appearance of active thymine degradation in these same cultures infected by the lipovirus suggests... the possibility that the missing genetic information is introduced by the lipovirus." The authors consider that the data are insufficient to exclude a second possibility that the genetic information for these catabolic enzymes is present in uninfected cells and that the degradation mechanism is "activated" by the lipovirus through enzyme induction, removal of suppressor gene, or removal of enzyme inhibitors.

D. Geraint James

925. **IDU Therapy of Herpes Simplex**

H. E. KAUFMAN, A. B. NESBURN, and E. D. MALONEY. *Archives of Ophthalmology [Arch. Ophthalm.]* 67, 583-591, May, 1962. 4 figs., 11 refs.

In this paper from Harvard Medical School and the Massachusetts Eye and Ear Infirmary, Boston, is described the successful treatment with 5-iodo-2'-deoxyuridine (IDU) of experimental keratitis produced by infecting rabbits' eyes with herpes simplex virus. Selected virulent strains of virus, freshly harvested from rabbit kidney or human amnion-cell cultures, were inoculated in a dose equal to at least a million times the infectious dose for the eye. One or 2 drops of a

0.1% solution of IDU were administered to infected eyes every 2 hours night and day, control animals receiving saline. Examiners were not told which were the treated animals and which the controls. Lesions were visible in the corneae of 137 control eyes within 12 hours and ulcers appeared in 24 hours; all the animals developed keratitis from which virus was isolated. IDU administered before infection prevented keratitis in 7 out of 7 eyes. When IDU was administered 2, 12, or 24 hours after infection, early lesions cleared, but half the eyes infected still developed small dendritic lesions. When IDU was administered at 48 hours its effect was dramatic, well-established lesions disappearing within a further 48 hours and symptoms of iritis also being abolished. Although lesions were cured in 6 out of 6 infected eyes treated at 48 hours, virus was still isolated from 2 of the 6 eyes, so that, recurrence was possible. Healing of the cornea was not inhibited by IDU.

IDU competitively inhibits the uptake of thymidine and therefore probably acts by suppressing the early deoxyribonucleic acid synthesis which occurs after infection of cells by herpes. After absorption IDU is rapidly dehalogenated in the body to form uridine. The authors stress that to inhibit virus multiplication and to compensate for absorption IDU must be present in the eye continuously.

Janice Taverne

926. Effect of *p*-Fluorophenylalanine on Psittacosis Virus in Tissue Cultures

Y. TANAMI and M. POLLARD. *Journal of Bacteriology* [*J. Bact.*] 83, 437-442, March [received May], 1962. 4 figs., 14 refs.

The inhibitory effect of *p*-fluorophenylalanine (FPA) on maturation of psittacosis virus was investigated, with attention to the time sequence of viral protein synthesis. Extracellular virus particles were not inactivated by FPA at a concentration of 100 μ g. per ml., at which level it interfered with maturation of intracellular virus. When FPA was added to infected tissue cultures earlier than 15 hours after infection, intracellular virus maturation was suppressed. However, when FPA was added after 15 hours, infective virus was produced, which indicates that the synthesis of an FPA-sensitive virus precursor (presumably viral protein) had already occurred. A latent ("dormant") infection of psittacosis virus, established in a medium deficient in phenylalanine and tyrosine, was also investigated.—[Authors' abstract.]

927. Observations on the Properties and Prevalence of Coe Virus

A. S. ABRAHAM. *Proceedings of the Society for Experimental Biology and Medicine* [*Proc. Soc. exp. Biol. (N.Y.)*] 109, 855-859, April [received June], 1962. 4 figs., 20 refs.

Coe virus was originally isolated from cases of acute respiratory disease in California; the isolation of a virus resembling it from material from Thailand led the author, at the University of Pittsburgh School of Medicine, Pennsylvania, to investigate its biological properties and compare them with those of the Thailand isolate. The resemblance of the Coe virus to the enterovirus group was confirmed, as also was its serological identity with Coxsackie A21 virus. The mean diameter of the virus particle was found to be $39.4 \mu\text{m} \pm 1.7 \mu\text{m}$. Indirect evidence showed that it contained ribonucleic acid, and a one-step growth curve indi-

cated that virus began to appear in the supernatant fluid 44 hours after inoculation. The yield per cell was about 100 plaque-forming units; this is in the lower range found with enteroviruses in monkey-kidney cells. Serum neutralization tests carried out on various population groups revealed significant antibody titres in 2% of children, 5.2% of young adults, and 12.1% of middle-aged adults. No significant levels of antibody were found in sera from Thailand, whereas 10 of 39 sera (age unspecified) from Japan showed titres signifying past exposure to Coe virus.

J. E. M. Whitehead

928. Viruses of Human Diseases

C. H. STUART-HARRIS. *British Medical Journal* [*Brit. med. J.*] 1, 1779-1788, June 30, 1962. 1 fig., bibliography.

BACTERIA

929. Occurrence of Penicillin-resistant Staphylococci in Patients Receiving Penicillin Orally for Prophylaxis of Recurrences of Rheumatic Fever

T. N. HARRIS, S. FRIEDMAN, K. A. HALLIDIE-SMITH, L. L. CORIELL, and D. FABRIZIO. *American Journal of Medicine* [*Amer. J. Med.*] 32, 545-551, April, 1962. 7 refs.

The authors studied the incidence of penicillin-resistant staphylococci in throat cultures from children who had had rheumatic fever and were maintained on prophylactic penicillin. Throat swabs were cultured on a brain-veal agar containing 5% defibrinated human whole blood at 37°C. for 48 hours. Colonies of staphylococci were subcultured for coagulase tests, antibiotic sensitivity, and bacteriophage typing.

Of 125 rheumatic patients receiving penicillin prophylaxis 71 (57%) were carrying coagulase-positive staphylococci. Of 45 similar patients not receiving penicillin 13 (29%) were carriers, while of 100 non-rheumatic patients at other hospitals only 8 were carriers of coagulase-positive organisms. About half (10) of the rheumatic patients given antibiotics but only one-third of those not receiving them harboured penicillin-resistant strains of staphylococci. These resistant organisms were found in 8 of the 100 non-rheumatic patients and in 5 out of 61 healthy school-children. The distribution of staphylococci phage group III was similar; of the children receiving antibiotics 37% were carriers of this phage type compared with 25% of those not given antibiotics and less than 7% of each of the control groups. This phage group was the predominant one in the hospital.

It is concluded that prophylactic penicillin results in the maintenance of a source of resistant strains of staphylococci in the community.

A. E. Wright

930. Concurrent Appearance of Oleandomycin- and Neomycin-resistant Staphylococci. [In English]

E. JANSSON and O. WAGER. *Annales paediatricae Fenniae* [*Ann. Paediat. Fenn.*] 8, 129-137, 1962. 2 figs., 9 refs.

The results of an investigation at the Aurora Hospital, Helsinki, seem to suggest that neomycin may play some part in the origination of oleandomycin resistance of *Staphylococcus aureus*. Over 1,500 strains of coagulase-positive staphylococci isolated from in-patients (946 strains), nursing staff (398 strains), and out-patients (202 strains) were tested for resistance to neomycin, oleandomycin, and erythromycin.

Neomycin was used fairly commonly in hospitals in Finland as well as outside the hospitals. Oleandomycin, on the other hand, was little used and then usually combined with tetracycline as "sigmamycin". Erythromycin was, however, commonly employed.

Of the strains resistant to oleandomycin, 17% were found to be resistant to neomycin and 8% to erythromycin. Of strains resistant to neomycin, 54% were resistant to oleandomycin and 9% to erythromycin. The corresponding figures for erythromycin-resistant strains of the staphylococci were appreciably higher.

The authors claim the simultaneous occurrence of oleandomycin and neomycin resistance not only in hospital in-patients, but also in out-patients, even though oleandomycin was little used. They consider that the reason for neomycin resistance lies in its frequent use, especially in the form of "naseptin" (neomycin and chlorhexidine) cream for the treatment of carriers of staphylococci, and that this use of neomycin contributed to the appearance of oleandomycin-resistant strains of *Staph. aureus*. A. E. Wright

931. Investigation of the So-called Pathogenic *Escherichia coli* in the Stools of Healthy and Sick Adults. (Ricerca dei cosiddetti coli patogeni nelle feci di adulti sani e malati) L. CAPOCACCIA and G. MUNGELLUZZI. *Archivio italiano di scienze mediche tropicali e di parasitologia* [Arch. ital. Sci. med. trop.] 43, 11-22, Jan. [received May], 1962. 20 refs.

When the faeces of 230 subjects (39 healthy, 74 with digestive disturbances but without diarrhoea, and 127 with enterocolitis) were examined for *Escherichia coli* at the Institute of Tropical Diseases, University of Rome, the organism was isolated from 10 patients, all of whom had enterocolitis. In 9 cases the organisms grew only on MacConkey's medium and in 9 cases they gave typical biochemical reactions. All 10 patients were sensitive to polymyxin and chloramphenicol and all had agglutinating antibodies in the sera (in titres of 1:12 to 1:96) against the *Esch. coli* isolated from the faeces. The organisms disappeared from the faeces when the patients were clinically cured. The *Esch. coli* isolated were of the serotypes O26, B26; O127, B8; O55, B5; O128, B12; O126, B16; O111, B4. The authors suggest that these types of *Esch. coli* may be pathogenic in adults. M. Lubran

SEROLOGY AND IMMUNOLOGY

932. Studies in Molecular Pathology. I. Localization and Pathogenic Role of Heterologous Immune Complexes R. C. MELLORS and W. J. BRZOSKO. *Journal of Experimental Medicine* [J. exp. Med.] 115, 891-902, May 1, 1962. 18 figs., 21 refs.

This paper from the Hospital for Special Surgery, Philip D. Wilson Research Foundation, New York, describes the localization of heterologous immune complexes following injection in mice and the concurrent development of membranous glomerulonephritis.

Crystalline bovine serum albumin (BSA) and hen ovalbumin (OA) were used as antigens, and antisera were raised in the rabbit (RAB). Fluorescent antigen (BSA* and OA*) and fluorescent antibody (RAB*) were obtained by the conjugation of each antigen and a crude gamma-globulin fraction of RAB with fluorescein isothiocyanate. BSA and OA

conjugated with lissamine rhodamine were also used. Various soluble fluorescent immune complexes were prepared by the addition of RAB to BSA* and OA*, and one with paired labels by adding lissamine-rhodamine-labelled BSA* to fluorescein-labelled RAB*.

Sterile materials were injected intravenously and tissues obtained for fluorescent microscopy and histology at 4 and 48 hours following the final injection. Four hours after multiple injections, fluorescent immune complexes containing BSA* or OA* or RAB* were localized in the reticulo-endothelial cells and polymorphs of the hepatic and splenic sinusoids, in the capillary endothelium of the heart and lungs, and in the renal glomerular basement membrane and tubules. At 48 hours after injection the complexes had almost disappeared from the splenic red pulp and liver and were localized in the splenic germinal centres and in the renal glomeruli. A membranous glomerulonephritis had by now developed and the affected animals had proteinuria.

The localization of the fluorescent antigens BSA* and OA* differed from that of the immune complexes. At 4 hours BSA* was present in the glomeruli, but OA* was poorly localized. At 48 hours both were inconspicuous and a glomerulonephritis did not develop.

The authors conclude that "the selective physical retention of proteins by structures comprising the glomerular ultra-filters" is of pathogenic significance in this form of experimental nephritis, and possibly also in membranous glomerulonephritis in man. Hewett A. Ellis

933. Antibody Production by Hypogammaglobulinemic Patients

S. BARON, J. P. NASOU, R. M. FRIEDMAN, G. M. OWEN, H. B. LEVY, and E. V. BARNETT. *Journal of Immunology* [J. Immunol.] 88, 443-449, April, 1962. 5 figs., 25 refs.

It has been reported that viral neutralizing substances with some properties of true antibody can be demonstrated in the serum of patients with hypogammaglobulinaemia. In this paper from the National Institutes of Health, Bethesda, Maryland, the authors describe the antigenic response to an intramuscular injection of 10 ml. of a trivalent poliomyelitis vaccine, followed by 1 ml. of vaccine 2 to 5 weeks later, in 4 patients with serum γ -globulin levels ranging from 73 to 300 mg. per 100 ml., and discuss the character of the serum factor responsible for viral neutralization.

Neutralizing activity against poliomyelitis virus could sometimes be detected by the standard metabolic inhibition test but was more often detected by the highly sensitive immuno-inactivation plaque neutralization test. Neutralization of virus was time-dependent and was not reversed by dilution; the activity was stable at 56° C. for 30 minutes and was located almost exclusively in the 7S γ -globulin fraction of serum. Following the vaccine inoculations, poliomyelitis virus neutralizing activity often appeared or was stimulated, but the final titre for each type remained abnormally low.

In 3 patients with serum γ -globulin levels approaching nil some viral neutralizing activity could be detected by the highly sensitive test; it neutralized virus directly, was not reversed by dilution, and was heat-stable.

In the authors' view these results suggest that "hypogammaglobulinaemic and agammaglobulinaemic" patients are able to produce antibody to a variety of antigens but only in abnormally small amounts". A. Ackroyd

Pharmacology and Therapeutics

934. **A Case of Death from Necrotic Nephrosis during Chlorpromazine Therapy.** (Случай смерти от некротического нефроза при лечении аминазином)

JA. O. OL'ŠANSKIĭ and V. V. MOROZOV. *Журнал Невропатологии и Психиатрии* [Zh. Nevropat. Psikhiat.] 62, 762-764, No. 5, 1962. 1 fig., 4 refs.

A 38-year-old female schizophrenic was given chlorpromazine in doses increasing to 200 mg. daily. Before administration there had been no anaemia, increase in erythrocyte sedimentation rate, or hypertension. Traces of albumin in the urine had been found only twice during her 13 years' stay in hospital. On the 38th day of treatment with chlorpromazine she developed facial oedema, breathlessness, cyanosis of the lips, rapid pulse, and moderate hypertension. The urine, scant in volume, contained nearly 6 g. of albumin per 100 ml., epithelial cells, polymorphonuclear leucocytes, erythrocytes, and hyaline and granular casts. Pulmonary oedema and extreme oliguria developed and the patient died on the 41st day after treatment started. At necropsy the kidneys were soft and swollen, and on section yellowish-grey with scattered haemorrhages in cortex and medulla. The capsule was adherent in places to the kidney substance. Microscopy showed swelling of the glomerular tufts. The cells of the convoluted tubules contained fine granules and in most cases their nuclei had disappeared. The epithelium of the few surviving tubules was flattened and the lumina widened. The collecting tubules contained many hyaline casts. Dilatation and stasis were seen in the vessels. The authors consider that some of the histological findings suggest that chronic kidney disease had been present, but that the patient's final acute illness was connected with the administration of chlorpromazine. G. P. McGovern

935. **The Evaluation of a New Cough Suppressant, "Detigon", in General Practice**

P. R. NOEL. *British Journal of Diseases of the Chest* [Brit. J. Dis. Chest] 56, 70-77, April, 1962. 1 fig., 10 refs.

The efficacy of a new cough suppressant, "detigon" (chlorphedianol hydrochloride), was studied at the Clinical Investigation Unit of the Huntingdon Research Centre, Huntingdon.

The drug was assessed by an experimental method in human volunteers and by a double-blind clinical trial in patients in general practice. In the experimental method 10 healthy volunteers were tested on 4 days with 29 mg. (20 drops) of detigon (on 2 days), 11 mg. of codeine in an identical vehicle, and a 50-mg. tablet of ascorbic acid. The subjects chose the order of administration, but did not know which preparations contained the drug being tested. The number of coughs produced by inhalation of a 15% aerosol of citric acid before and again one hour and 2½ hours respectively after administration of the drugs were recorded. At one hour there was 55% inhibition of induced coughs after taking detigon, compared with 18% after codeine and no inhibition after ascorbic acid. After 2½ hours there was 33% suppression in response to the first trial of detigon and 17% in response to the second, compared with 18% after

codeine. The difference between the inhibition produced by detigon and that produced by codeine was statistically significant at one hour and (in the first trial) at 2½ hours.

In a clinical trial 130 patients (65 male and 65 female) received 29 mg. of detigon and 109 (52 male and 57 female) received 22 mg. of codeine (double the dose tried in the experimental method), each drug being given 6-hourly. The results were assessed over the first 3 days' treatment. Antitussive action was noted in 79% of the patients receiving detigon and in 84% of those receiving codeine; the action was pronounced (moderate or marked on a 3-point scale) in 50% of patients given detigon. Side-effects (evaluated from the answers to direct questions) were recorded in 41% of patients with detigon and in 52% with codeine; the incidence of drowsiness in patients given codeine was twice that in patients on the trial preparation.

The author concludes that detigon is a highly effective cough suppressant when given in the dosage recommended for adults (up to 20 drops 4 times daily). R. H. Cawley

936. **Mercurial Diuretics.** [Review Article]

M. F. LEVITT and M. H. GOLDSTEIN. *Bulletin of the New York Academy of Medicine* [Bull. N.Y. Acad. Med.] 38, 249-263, April, 1962. 4 figs., bibliography.

937. **Suppression of the Pituitary-ACTH Response in Man by Administration of ACTH or Cortisol**

J. E. PLAGER and P. CUSHMAN JR. *Journal of Clinical Endocrinology and Metabolism* [J. Clin. Endocr.] 22, 147-154, Feb., 1962. 6 figs., 25 refs.

Adrenal insufficiency following cessation of adrenal steroid therapy is thought to be secondary to inhibition of pituitary function. Since there is as yet no satisfactory method of measuring pituitary adrenocorticotrophin (ACTH) the authors of this paper from the University of Rochester School of Medicine and Dentistry, New York, used "metopirone" (SU 4885), the 11β-hydroxylase inhibitor, to assay pituitary responsiveness. The patients (males aged 20 to 45 years) were convalescent from minor surgical operations and showed no evidence of endocrine, renal, or hepatic disorders. Responsiveness was assessed 48 hours after 3 days' treatment with ACTH or cortisol by measuring the plasma levels of cortisol and of substance S (17α:21-dihydroxy-4-pregnene-3:20-dione) following an infusion of metopirone and metopirone in combination with ACTH. It was found that in patients pre-treated with ACTH there was decreased endogenous release of pituitary ACTH and in those given cortisol there were both decreased pituitary and decreased adrenal responsiveness.

It is suggested that since the pituitary-ACTH response is decreased by ACTH therapy this may limit the value of ACTH as an adjuvant during withdrawal of corticosteroids.

[The method used was a modification of that previously described by Plager *et al.* (J. clin. Invest., 1961, 40, 1315) and the original paper should be consulted for details.]

B. M. Ansell

Chemotherapy

938. Pyruvate Metabolism in Epileptic Tuberculous Patients. [In English]

R. C. R. BARRETO, S. O. SABINO, and R. S. BITTENCOURT. *Experientia [Experientia (Basel)]* 18, 280-281, June 15, 1962. 1 fig., 7 refs.

Isoniazid is especially toxic in epileptic tuberculous patients. It combines with pyruvate to form a hydrazone, and the consequent lowering of the blood pyruvate level causes convulsions. This has been confirmed in 3 epileptic tuberculous patients by the present authors, working at the University of Brazil, Rio de Janeiro. Each convulsion was followed by a gradual decline in blood pyruvate level from high values towards normal, and when the next fit occurred the level rose sharply again. Cessation of isoniazid treatment lengthened such "cycles" from 3, 4, or 5 to 7 days and raised the range of the blood pyruvate levels. An oral dose of 200 mg. of sodium pyruvate twice daily further reduced the frequency of convulsions.

T. B. Begg

939. Isolated Regional Perfusion in Treatment of Malignant Disease

O. GARAI, C. COOLING, and D. STAUNTON. *British Medical Journal [Brit. med. J.]* 1, 1231-1235, May 5, 1962. 4 figs., 13 refs.

Working at the Royal Marsden Hospital, London, the authors have used isolated regional perfusion with melphalan (PAM) or mustine (nitrogen mustard, HN2) in the treatment of 14 patients with tumour in the leg, 2 with adenocarcinoma of the rectum, and 2 with squamous-cell carcinoma of the uterine cervix. In general the method followed was that introduced by Creech *et al.* (*Ann. Surg.*; 1958, 148, 616; *Abstr. Wld Med.*, 1959, 25, 317). The lower limb or pelvis is isolated from the rest of the body by tourniquet, the relevant artery and vein cannulated, and perfusion maintained by a pump oxygenator system. Leakage to the general circulation is estimated by means of ⁵¹Cr-labelled erythrocytes or ¹³¹I-labelled human serum albumin. Melphalan or mustine is then added and the perfusion continued, for 60 minutes in the case of melphalan and for 35 minutes with mustine. The doses used have ranged from 35 to 100 mg. of melphalan and from 30 to 35 mg. of mustine.

In 5 of the 14 patients with leg tumour (13 with melanoma and one with fibrosarcoma) the tumour has either disappeared or is still regressing. In 4 cases the method was followed by excision and no recurrence has yet been seen, though serious gangrene occurred in one leg. Of the 4 patients treated by pelvic perfusion relief of pain was obtained by all; however, one died from peritonitis, and temporary tumour regression was seen only in one. Complications of the technique have been few. Bone-marrow depression may occur and can be a particularly serious hazard in pelvic perfusion, in which it is difficult to prevent leakage of the drug into the general circulation. A reaction occurs in the tumour, often in 48 hours, when it shows a red halo of inflammation, followed by a mild purulent reaction.

K. E. Halnan

ANTIBIOTICS

940. Penicillin Antibody in Maternal and Cord Bloods and Its Possible Relationship to Hypersensitivity

M. EPP. *Immunology [Immunology]* 5, 287-294, March [received May], 1962. 1 fig., 17 refs.

This paper from the University of Saskatchewan, Saskatoon, Canada, describes a contributory study to the problem of penicillin hypersensitivity in which penicillin antibodies in maternal blood and cord blood were determined by two methods. In the first, serum was tested for antibodies by the agglutination of erythrocytes to which *para*-aminobenzyl penicillin had been linked by the use of bis-diazotized benzidine (BDB). In the second, the Ley method, erythrocytes were mixed with benzylpenicillin. The serum for testing was separated from the infants' blood taken from the placental end of the umbilical cord just after delivery and from maternal venous blood taken 3 days after parturition. In all, 105 paired samples of maternal and cord blood serum were examined by both methods. The sera of the 3 mothers who were known to be allergic to penicillin showed antibodies to the antibiotic by both methods, whereas the cord blood sera in these cases showed antibodies only with the Ley method. Of the other 102 mothers 65 had been treated with penicillin without adverse effects and in 63 of these the BDB test showed antibodies in the serum. A further 10 mothers were uncertain about previous penicillin treatment, and of these 6 showed antibodies in their sera with the BDB test. The remaining 27 mothers had not been treated with penicillin and the BDB test revealed antibodies in the sera of 24 of these. This test revealed no antibodies in the cord blood sera except in those of the infants of 2 mothers who had not been treated with penicillin.

In contrast, the Ley test revealed antibodies in the sera of 97 of the 102 mothers who had never shown an allergic reaction to penicillin and in the cord blood sera of 75 of their infants. The author considers that the two tests measure antibodies to penicillin with different specificities. She suggests that those measured by the Ley test are transferred across the placenta, whereas those measured by the BDB haemagglutination test appear to be unable to pass the placental barrier.

Charles Rolland

941. Ampicillin: a Broad-spectrum Penicillin

J. A. P. TRAFFORD, D. M. MACLAREN, D. A. LILICRAP, R. D. S. BARNES, J. C. HOUSTON, and R. KNOX. *Lancet [Lancet]* 1, 987-990, May 12, 1962. 11 refs.

The authors describe 62 patients (41 with urinary infections, 15 with chest infections, 5 with wound infections, and one a carrier of *Salmonella typhi*) treated at Guy's Hospital, London, with ampicillin (6[D(-)- α -aminobenzyl] penicillin). The dosage was 0.5 to 1.0 g. 4 times daily for 5 to 7 days. The drug was found to be effective against a range of Gram-negative organisms. Of the 41 cases of urinary infection, 27 were due to organisms shown to be sensitive to the drug *in vitro*; in 24 of these (89% of the 27 and 58% of the 41), the result was successful. All of 5 patients with chest

infections due to *Haemophilus influenzae* responded satisfactorily. In the treatment of wound infections the drug was less successful. All infections due to organisms of the *Klebsiella* group were resistant to the drug; these strains produced penicillinase, which readily degrades ampicillin. Toxic reactions were minimal; they were observed in only 5 of the 62 cases treated and were similar to those seen with other penicillins.

F. W. Chattaway

942. **Pharmacology and Chemotherapy of Ampicillin—a New Broad-spectrum Penicillin**

P. ACRED, D. M. BROWN, D. H. TURNER, and M. J. WILSON. *British Journal of Pharmacology and Chemotherapy* [Brit. J. Pharmacol.] 18, 356–369, April, 1962. 6 refs.

The pharmacology and chemotherapy of ampicillin, 6[b(–)- α -aminophenylacetamido] penicillanic acid, are described in this paper from the Beecham Research Laboratories, Betchworth, Surrey. This new penicillin was found to have low toxicity for mice and rats in acute experiments and also for rats and dogs on prolonged administration. After oral administration it produced higher blood levels than did phenoxymethylpenicillin. The highest blood level occurred one hour after oral administration. On intramuscular injection the blood levels obtained with ampicillin and phenoxymethylpenicillin were similar, although at one hour the blood level obtained with the latter was higher. The distribution of ampicillin in the body was similar to that of other penicillins. The drug was found to be excreted unchanged in the bile and urine, although after oral administration a large proportion was destroyed in the intestine, presumably by penicillinase. It is not metabolized within the body. Absorption studies indicated that the rat is an unsuitable animal for the investigation of oral absorption of penicillin derivatives.

Ampicillin is reported to be effective in experimental infections due to *Staphylococcus pyogenes* (penicillin-sensitive), *Streptococcus pyogenes* Group A, *Diplococcus pneumoniae*, *Salmonella typhimurium*, and *Klebsiella pneumoniae*. Against penicillin-sensitive staphylococci (*Staph. aureus*, Smith), ampicillin, benzylpenicillin, and phenethicillin were the most active antibiotics tested when given subcutaneously; when given orally, ampicillin, phenoxymethylpenicillin, and phenethicillin were equally active. Ampicillin was inactive against staphylococci resistant to benzylpenicillin. Against streptococci, ampicillin, phenoxymethylpenicillin, phenethicillin, and tetracycline were all very active orally or subcutaneously. Ampicillin was more active against pneumococci than phenoxymethylpenicillin, phenethicillin, and benzylpenicillin. Against the Gram-negative organisms *Klebsiella pneumoniae* and *Salm. typhimurium* ampicillin was active orally and subcutaneously, whereas benzylpenicillin, phenethicillin, and phenoxymethylpenicillin were inactive. The authors stress the importance of correlating the results *in vitro* with those *in vivo* in the assessment of new chemotherapeutic agents.

P. T. Main

943. **Vancomycin in Serious Staphylococcal Infections**

J. E. GERACI, D. R. NICHOLS, and W. E. WELLMAN. *Archives of Internal Medicine* [Arch. intern. Med.] 109, 507–515, May, 1962. 13 refs.

The properties of vancomycin are discussed and the results obtained with this antibiotic at the Mayo Clinic in the treatment of 85 patients with serious staphylococcal infections

are reviewed. Vancomycin is bactericidal in small amounts (4 μ g. per ml. of medium) for both benzylpenicillin-sensitive and benzylpenicillin-resistant strains of staphylococci. It inhibits non-haemolytic streptococci and also enterococci. The toxicity of the antibiotic is relatively low, but in fairly high concentration it may cause nerve deafness; and for this reason the blood levels should usually not exceed 30 μ g. to 40 μ g. per ml. It must be given intravenously in serious infections. With a dosage of 0.5 g. every 6 hours there is some accumulation of the drug, the serum levels being 13 μ g. to 15 μ g. per ml. 3 hours after administration; dangerous levels could be reached with this dosage in patients with impaired renal excretion. It is therefore advised that in the treatment of serious staphylococcal infections 1 g. of vancomycin should be given intravenously 6-hourly for one or 2 days and 1 g. every 12 hours thereafter, blood levels being determined daily. It diffuses readily into the serous synovial cavities and across the inflamed meninges.

Vancomycin was given with success in 85 cases of serious staphylococcal infections, which included 19 cases of endocarditis (mostly postoperative), 15 of septicaemia, 13 of soft-tissue infections, 4 of meningitis, 2 of epidural abscess, one of cavernous sinus thrombosis, 7 of pneumonia, 7 of bone and joint infections, 7 of ileocolitis (for which it is likely to be life-saving since it appears in high concentration in the faeces), 5 of empyema, 4 of furunculosis, and one of post-operative parotitis. The authors state that the duration of treatment is likely to be 3 to 6 weeks in cases of endocarditis and in those of septicaemia or bone and joint infections combined with focal lesions, and one to 2 weeks in other conditions. There is no indication for combining vancomycin with other antibiotics.

In an addendum to this [excellent] paper the authors state that it was submitted before reports on methicillin and oxacillin treatment of staphylococcal infections were published, and that vancomycin would now be the second choice for the treatment of serious staphylococcal infections. It would be suitable for penicillin-sensitive patients and those who cannot take the new biosynthetic penicillins.

H. Stanley Banks

944. **The Use of Amphotericin B in Man**

V. T. ANDRIOLE and H. M. KRAVETZ. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 269–272, April 28, 1962. 18 refs.

Amphotericin B is the only broad-spectrum antifungal agent at present available for the treatment of systemic mycotic infections in human beings. The results obtained with this drug in the treatment of histoplasmosis, North American blastomycosis, coccidioidomycosis, cryptococcosis, and *Candida* infections are discussed in this paper from the National Institutes of Health, Bethesda, Maryland. In most of these conditions the antibiotic has been found to be of value when administered intravenously or intrathecally. Considerable toxic reactions, which include fever, gastrointestinal disturbances, renal damage, and hypokalaemia, are common and measures to combat these, chiefly by giving the drug in a gradually increased dosage, are discussed. For effective intravenous therapy the dosage is 1 mg. per kg. body weight on alternate days, continued until a total dosage of 3 g. has been given. Intrathecally the dosage is usually 0.5 mg. 2 or 3 times a week to a total dosage of the order of 15 mg.

F. W. Chattaway

Infectious Diseases

VIRUS DISEASES

945. Rubella and Congenital Cataract Blindness

J. SIGURJONSSON. *Medical Journal of Australia* [Med. J. Aust.] 1, 588-590, April 21, 1962. 7 refs.

The author has previously shown (*Amer. J. med. Sci.*, 1961, 242, 712) that after the two largest epidemics of rubella on record in Iceland (1940-1 and 1954-5) 6 and 8 children respectively were born deaf, while in non-epidemic years not more than one or 2 such births occurred. Congenital cataract is more difficult to trace from institutional data and registers for the blind, since it is often amenable to surgical treatment. Information was, however, obtained from the ophthalmologists in Iceland for the period 1941-60; 19 cases were traced, of which 4 were closely grouped in 1955, about 7 months after the peak of the preceding rubella epidemic, and one followed in the wake of the 1940-1 epidemic. All the mothers gave a history of rubella in the earliest months of pregnancy. The ratio of congenital deafness to blindness was thus about 2.8:1 for these two epidemics—a similar figure to that obtained in Australia by Swan and colleagues (*Med. J. Aust.*, 1946, 2, 889). Five additional cases of congenital cataract were connected with rubella in the 20-year period, and all but one of these 10 children also had a heart defect. Although the risk of cataract blindness in Iceland was apparently lower than that of deafness (5% to 10% of females infected with rubella in the first trimester of pregnancy), rubella had probably been the most frequent cause of congenital blindness from cataract in the 20-year period considered.

H. Stanley Banks

946. Poliomyelitic Paralysis and Tonsillectomy Reconsidered

R. T. RAVENHOLT. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 103, 658-668, May, 1962. 25 refs.

An epidemiological survey of 111 cases of paralytic poliomyelitis occurring in King County, Seattle, Washington, in 1959 showed that the number of cases of bulbar involvement among those whose tonsils had been removed was not greater than would be expected by chance. This remained true for all age groups. It was further noted that in an earlier epidemic in the area in 1952 there was the same chance proportion of cases of bulbar involvement after tonsillectomy.

This finding in two epidemics separated by 7 years and occurring respectively before and after the introduction of the Salk vaccine is considered to be significant. It contrasts with the reported observations of others, which are reviewed, that the bulbar paralytic form of poliomyelitis occurs more frequently in patients who have undergone tonsillectomy than in those who have not, but there is considerable variation in the figures. It is suggested that the relationship between previous removal of the tonsils at any time and the development of bulbar paralysis is not merely a straightforward one of cause and effect.

E. H. Johnson

947. A Clinical and Epidemiological Study of Infective Hepatitis, with Special Reference to Two Small Epidemics. (Klinische und epidemiologische Studien zur Hepatitis epidemica aus Anlass einiger Kleinraumepidemien)

H. RADL, W. BOSTJANCIC, and S. GRUBMÜLLER. *Archiv für Kinderheilkunde* [Arch. Kinderheilk.] 166, 127-148, May, 1962. 1 fig., bibliography.

Between September, 1960, and August, 1961, 151 children (80 boys and 71 girls, aged 3 to 14 years) with infective hepatitis were observed at the Wilhelminenspital, Vienna (compared with 160 between 1952 and 1960); 61 were admitted from their own homes in a village in Lower Austria and from Vienna itself, the remainder from 2 children's homes near the capital. The maximum incidence of the disease in 1961 occurred between January and May, with a peak in March. The chief symptoms were malaise, loss of appetite, nausea and vomiting, with headache, abdominal pain, constipation, diarrhoea, and fever. The chief signs were tenderness and enlargement of the liver, furred tongue, icterus of skin and conjunctivae, bile in the urine, and pale stools. One 11-year-old patient had neck rigidity and sluggish reflexes, but was afebrile, when admitted to hospital; the cerebrospinal fluid (C.S.F.) contained 85 cells; 2 days later jaundice appeared and 10 days later the C.S.F. was normal. Enlarged spleen and lymph nodes, fleeting limb pains, and exanthem were rare. Haemorrhagic diathesis was not noted. Jaundice lasted 4 to 20 days. There were no deaths. The serum levels of glutamic-pyruvic transaminase, glutamic-oxalacetic transaminase, and bilirubin were raised but fell to normal within 5 weeks; the thymol turbidity, however, was still high at that time. Treatment was symptomatic. Prognosis was favourable. The authors consider that this disease is less contagious than measles. Differential diagnosis is helped by epidemiological information and is less difficult in children than in adults.

[Despite its length, this paper establishes nothing new. Virological studies, where possible, would be of much interest in future investigations of this disease.]

I. M. Librach

948. Symposium on Viral Hepatitis. Epidemiologic Patterns of Viral Hepatitis

R. W. MCCOLLUM. *American Journal of Medicine* [Amer. J. Med.] 32, 657-664, May, 1962. 1 fig., 35 refs.

949. Enteroviruses in Infantile Diarrhoea in India. Part I. Investigations Carried Out in Bombay

V. P. CHANDRA. *Indian Journal of Medical Research* [Indian J. med. Res.] 50, 343-347, May, 1962. 7 refs.

Evidence is accumulating that, in addition to bacteria, the E.C.H.O. viruses may be responsible for some cases of summer diarrhoea in infants. In an investigation carried out over a 15-month period in India, where diarrhoea in infants is one of the major causes of infant mortality, 13 agents cytopathogenic to monkey kidney cells were isolated from rectal swabs taken from 100 infants under 2 years of age who had been admitted to hospital suffering from

diarrhoea, whereas only 4 cytopathogenic agents were isolated from 140 children from the same locality and of the same age group and socio-economic status who had been admitted with conditions not affecting the gastro-intestinal tract.

In the control group, 2 of the viruses were identified as being polio Type III, one as E.C.H.O. Type 7, and the other could not be identified; in the cases of diarrhoea 2 viruses were identified as being E.C.H.O. Type 7, 2 as E.C.H.O. Type 13, and one as polio Type II, while 5 were untypable and 3 could not be identified. The only antisera available were those against the polioviruses, E.C.H.O. Types 1 to 14, and Coxsackie Types A9 and B1 to 5. Most of the isolations occurred during the monsoon months of July and August, the period of highest incidence of cases of infantile diarrhoea.

In a simultaneous serological survey, antibodies against E.C.H.O. Type 7 were found in the sera of all 20 mothers tested before delivery, in the cord blood of 17 of their infants, and in the sera of 15 out of 20 healthy infants aged between 7 and 30 months; antibodies against E.C.H.O. Type 13 were found in 16 of the mothers, 7 cord bloods, and 12 of the infants.

A. Ackroyd

BACTERIAL DISEASES

950. *Pasteurella pseudotuberculosis* Infections in Man. (Die Pseudotuberkulose des Menschen)

W. MASSHOFF. *Deutsche medizinische Wochenschrift* [Dtsch. med. Wschr.] 87, 915-920, May 4, 1962. 47 refs.

Pasteurella pseudotuberculosis is most often seen in rodents, but also affects domestic animals and birds. When the disease occurs in man it assumes either a septic form with typhoid-like symptoms or a more benign form with intestinal symptoms. The latter is the form usually found in young people.

In this paper from the Free University, Berlin, the author discusses in detail the pathogenesis of the intestinal form of pseudotuberculosis, but notes that the difference between the two forms of the disease is only one of degree. The pathological changes are limited to the last portion of the ileum, which was usually found to be thickened, oedematous, and inflamed, while many swollen, infected lymph nodes were seen in the ileocaecal angle. These changes are those resulting from an enteric infection. Experiments on guinea-pigs are also described, and the changes appearing at the point of infection are compared with those seen elsewhere after lymphogenous and haematogenous spread. Nosologically, the author discusses the grounds for classifying the disorder as "an abscess-forming reticulocytic ileocaecal lymphadenitis". He does not agree that there is any relationship between Crohn's disease and intestinal pseudotuberculosis.

Franz Helmann

951. *Pasteurella pseudotuberculosis* Antibody Titres in Man: a Preliminary Report

S. I. HNATKO and A. E. RODIN. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 725-727, April 21, 1962. 11 refs.

In recent years a number of studies have been made of human infections with *Pasteurella pseudotuberculosis*. This organism is primarily an animal pathogen, but may in man

produce either (1) an acute septicaemia which resembles enteric fever or tuberculosis, or (2) mesenteric lymphadenopathy which clinically may closely mimic acute appendicitis. It is therefore desirable to be able to diagnose such cases before laparotomy is undertaken; the detection of antibodies to the live-smooth variants of the organism has been the most promising line of approach hitherto. A rise in antibody titre for 3 weeks after the onset of the disease, which is followed by a decline to zero 5 months later, has been reported.

This paper from the University of Alberta describes an investigation for the presence of *Past. pseudotuberculosis* antibody in 21 consecutive cases in which the clinical diagnosis was acute appendicitis. The organisms employed were two serologically distinct strains of *Past. pseudotuberculosis*, one presumably of Type I and one of Type IV. The agglutination tests were carried out on living suspensions of these organisms; these were incubated at 37° C. for 4 hours, left in the refrigerator overnight, and the results read the next morning.

Of the 21 cases studied, the diagnosis of acute appendicitis was confirmed in 16. In one of the remaining 5 cases enlarged mesenteric lymph nodes were found; in this case there were no detectable antibodies. The sera from 2 cases gave a positive agglutination reaction against the Type-I strain to titres of 1:120 and 1:240 respectively; in the first case gangrenous appendicitis with perforation was revealed at operation, while in the second case a normal appendix was found.

The authors conclude that the presence of agglutinins to *Past. pseudotuberculosis* "is not necessarily an indication of acute infection, unless the titres are markedly elevated and progressive".

John M. Talbot

952. Efficacy of a Single Intravenous Injection of Pyrrolidinomethyltetracycline in Pneumococcal Pneumonia: Report of 20 Cases with Assays of 24 Hour Antibiotic Activity in Serum

B. M. LIMSON and R. B. GUEVARA JR. *Antibiotics and Chemotherapy* [Antibiot. and Chemother.] 12, 85-90, Feb. [received May], 1962. 6 figs., 11 refs.

Pyrrolidinomethyltetracycline is an aminomethyl derivative having an antibacterial spectrum and an efficacy *in vitro* identical to those of the parent substance tetracycline, but therapeutic levels in blood and urine persist for as long as 24 hours after a single intravenous dose equivalent to 250 mg. tetracycline hydrochloride. The drug should be injected intravenously at the slow rate of 1 to 3 minutes per single dose; side-reactions—flushing of face, feeling of warmth, and dizziness—may occur for some 10 minutes after the injection, but these are usually abolished if the injection is made over a period of 3 minutes.

The results of a single intravenous injection of 275 mg. (equivalent to 250 mg. tetracycline) in uncomplicated pneumococcal lobar pneumonia in 20 patients were entirely comparable to those obtained with conventional repeated doses of various antibiotics given by mouth or intravenously. No trial was made in complicated pneumonia or other more serious infections. Nevertheless it is suggested that a long-acting intravenous tetracycline which can be administered at 12- to 24-hour intervals would be a useful addition to the drugs employed in the treatment of infections.

H. Stanley Banks

953. Human Brucellosis in South Africa

L. SCHÜRRE. *South African Medical Journal* [S. Afr. med. J.] 36, 342-349, May 5, 1962. 1 fig., bibliography.

After a review of the history of human brucellosis in South Africa and brief consideration of the clinical and laboratory diagnosis of the disease, this paper, from the South African Institute for Medical Research, Johannesburg, assesses the incidence and distribution of brucellosis in that country.

Notification figures show a downward trend of the disease in the white and an upward trend in the non-white population. The minimum annual incidence of new cases during the period 1956-9 was estimated at 0.20 per 100,000 population. This estimate was based on a survey of specimens of blood and serum submitted to the Johannesburg laboratories of the Institute during that period and on the answers to a questionnaire sent to the doctors of patients with possible brucellosis. (In comparison, the official figure, based on notifications to the Department of Health, was 0.19 per 100,000.) The lowest agglutination titre regarded as significant was 1:100, the dilution range used being 1:50 to 1:400 with smooth formalized suspensions of *Brucella abortus* and *Br. melitensis* respectively. The prozone phenomenon was observed in 7 cases, the extent of blocking being 1:50 in 4 cases, 1:100 in one, and 1:200 in 2. In 14 attempted blood cultures, *Br. abortus* was recovered in 2 cases and *Br. melitensis* in one. [No details of these blood cultures are given.]

A high proportion of the cases originated from the Eastern Transvaal and South West Africa, where cattle and goats were the probable reservoir hosts. The majority (85%) of the patients whose occupations exposed them to the disease (veterinary surgeons, stock inspectors, cattle farmers, butchers, and laboratory workers) were white adults and in this group the diagnosis was made early in 63% of 116 cases. Only 14% of the cases unrelated to occupation were diagnosed in the initial stages. The disease often presents as obscure pyrexia, and early diagnosis was favoured by local epidemiological knowledge on the part of the general practitioners.

In January, 1959, a field study carried out in Sekukuni and (Eastern Transvaal) in 102 apparently healthy Africans and 40 African out-patients chosen at random [limited details only] showed hepatomegaly in 16, splenomegaly in 11, and splenohepatomegaly in 3. Agglutination tests performed on all the subjects, with serum dilutions ranging from 1:10 to 1:2,560, yielded 9 positive results, agglutination titres being 1:10 (7 cases), 1:40 (1), and 1:2,560 (1). The figures obtained in this limited study were regarded as consistent with the national figures. In conclusion, brucellosis in southern Africa is considered to be endemic and under-notified. Early diagnosis, treatment, and the recognized prophylactic measures are urged.

Kurt Schwarz

954. Observations and Results of Treatment in an Epidemic of Typhoid Fever. (Erfahrungen und Ergebnisse einer Typhusepidemie)

H. RUHLAND and W. SCHIEDEL. *Münchener medizinische Wochenschrift* [Münch. med. Wschr.] 104, 1077-1080, June 8, 1962. 6 figs., 25 refs.

The authors report on an epidemic of typhoid fever which occurred at Worms, Germany, and in the surrounding district in the summer of 1960. Of the 78 cases notified (48

in adults and 30 in children), 52 (34 adults and 18 children) were treated at the Worms City Hospital. The infection was traced to a typhoid carrier handling a special brand of bottled milk which, it was claimed, could safely be drunk fresh. Of the 52 patients 40 had drunk this milk and the 12 others had contracted the disease by contagion. One other case (bringing the series to 53), infected from another source, had been admitted to hospital before the outbreak. Positive blood cultures were obtained later than usual because the organisms grew very slowly in the bile medium used. The patients were treated with chloramphenicol, either alone (30 cases) or combined with cortisone (23 cases). The dosage of chloramphenicol varied between 40 and 150 mg. per kg. body weight. In a few cases glossitis appeared as a side-effect of this drug. In the 23 patients who received the combined treatment, chloramphenicol was given in the dosage mentioned above, while the total dosage of cortisone varied between 100 and 420 mg. for adults and 95 and 195 mg. for children. The use of cortisone hastened the fall in temperature (which in most of the cases took place within a few hours) and improved the general condition.

Franz Helmann

955. The Treatment of Tetanus

R. SLOME, P. M. SMYTHE, and H. A. BROWN. *Transactions of the College of Physicians, Surgeons and Gynaecologists of South Africa* [Trans. Coll. Physns S. Afr.] 6, 32-38, April [received June], 1962. 7 refs.

In the 10-year period 1952-61, 205 patients with tetanus were admitted to Groote Schuur Hospital, Cape Town. Among these were 58 neonates who were excluded from the present study because they constituted a special problem. From 1952 to 1956 the mortality was 48% and from 1957 to 1961 it was 28%. From January, 1958, tracheotomy and intermittent positive pressure respiration (I.P.P.R.) were used in the treatment of patients with tetanus and the results obtained in 50 cases are described. The portal of entry of the organisms was a wound in 22 cases and the uterus (post-abortion) in 18; in 10 there was no obvious wound and the site of entry was unknown. Tetanus was considered to be mildly severe in 6 cases, moderately severe in 11, and severe in 33—that is, with rigidity and either frequent and severe generalized spasms or laryngeal or pharyngeal spasms interfering with respiration. Tracheotomy was performed in 28 cases and I.P.P.R. was given in 9; in 13 cases tracheotomy was not carried out.

The value of this paper lies in the authors' discussion of the principles of treatment, including the indications for tracheotomy, I.P.P.R., and curarization. The difficulties encountered by the staff in giving I.P.P.R., which was then a new procedure at the hospital, are emphasized. The authors, while acknowledging that the results are not outstandingly good, consider that they are better than those obtained in earlier series in the same hospital. They are reported in the hope of "producing a greater awareness of the respiratory problems of tetanus and of the indications for tracheotomy and I.P.P.R. and the complications which result from these methods of treatment". Since this series was concluded better results have been obtained. The authors have no doubt that the greatest advance in the treatment of tetanus has come from the recognition that respiratory difficulty is the main cause of death. They have found that the prognosis in post-abortion cases is no worse than in severe cases due to other causes.

H. Stanley Banks

Tuberculosis

956. Nontuberculous Mycobacterial Infections in Children: a Preliminary Clinical and Epidemiologic Study
K. H. K. Hsu. *Journal of Pediatrics* [J. Pediat.] 60, 705-710, May, 1962. 1 fig., 18 refs.

The author, writing from the Jefferson Davis Hospital, Houston, Texas, draws attention to the increasing recognition and prevalence of infections by mycobacteria (other than *Mycobacterium tuberculosis*) which hitherto have been classified as saprophytes. The disease caused by these mycobacteria simulates tuberculosis clinically and pathologically, but differs from it in epidemiology and in response to drug therapy. Mycobacterial infections can sensitize man to tuberculin, but a mycobacterial infection can be distinguished from a tuberculous infection by skin tests in which several types of specific antigen are used. Antigens made from purified protein derivative (P.P.D.) of mycobacteria have been prepared by the United States Public Health Service.

An account is given of 5 cases of chronic cervical lymphadenitis and one case of chronic skin ulcer of the cheek in children aged between 14 and 17 years. The organisms were recovered on culture in 4; in the other 2 the diagnosis rested on the results of P.P.D. skin tests and on the histology of the lymph nodes. Antituberculous chemotherapy was used in all cases, but (except in the cheek ulcer) the results were poor. Incision and drainage of the diseased lymph nodes was followed by persistent discharge, and only total excision was satisfactory. When these patients were tested with specific P.P.D. antigens, strongly positive skin reactions—stronger than with the standard P.P.D. prepared from *Mycobacterium tuberculosis*—were obtained in all cases. Skin testing with specific P.P.D. in 2 negro schools indicated a higher rate of infection by these mycobacteria than by tuberculosis. Until the mycobacterial P.P.D. antigens become generally available for differential testing, it should be remembered that the stronger the tuberculin reaction the more likely it is to be tuberculous in origin, while a weak reaction suggests the possibility of mycobacterial infection.

John Lorber

957. Treatment of Tuberculous Meningitis in Adults. (Résultats de la thérapeutique de la méningite tuberculeuse de l'adulte)
J. PERNOD, C. CHAMBATTE, J. BATIME, and J. KERMAREC. *Revue de tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 26, 205-227, Feb.-March [received June], 1962. 4 figs., 4 refs.

The authors report on 80 cases of tuberculous meningitis treated at the Military Hospital, Percy, France. Nearly all the patients were soldiers; 72 were aged between 19 and 25 and none was older than 45. The basis of the treatment was isoniazid, antibiotics and corticosteroids being added when necessary. The long-term results were: complete recovery, 39 cases (49%); mild sequelae compatible with normal activity, 27 cases (34%); serious sequelae constituting a grave social handicap, 10 cases (12%); death, 4 cases (5%). In the authors' opinion the administration of isoniazid in

high dosage, together with supportive therapy, especially corticosteroid drugs, has rendered intrathecal treatment unnecessary in the usual forms of this disease.

Norman F. Smith

RESPIRATORY TUBERCULOSIS

958. Pleurisy with Cholesterol Crystals. (Les pleurésies à cristaux de cholestérol)
J. GUILLERMAND, J. GROULADE, and D. ZIANE. *Poumon et le cœur* [Poumon] 18, 359-376, 1962. 5 figs., bibliography.

The authors, writing from Grenoble, France, describe 2 cases of pleural effusion with cholesterol deposits, and analyse reports of 57 cases in the literature. Cholesterol effusions are an interesting stage in the evolution of tuberculous serofibrinous pleurisy. They occur most frequently in cases in which the effusion is encysted and of long standing. Tubercle bacilli have been found in the fluid in 13.5% of the reported cases. The effusion, if untreated, usually persists indefinitely. Systemic antituberculous chemotherapy usually sterilizes the fluid, but decortication may be indicated if complications or severe respiratory embarrassment are present. The cholesterol may arise from the breakdown of lipoprotein complexes found in caseous matter.

Arnold Pines

959. A Comparative Study of the Metabolism and Toxicity of Isoniazid and Isoniazone Calcium Pyruvate
E. I. SHORT. *Tubercle* [Tubercle (Lond.)] 43, 22-32, March [received May], 1962. 3 figs., 7 refs.

Isoniazone calcium pyruvate is a hydrazone derivative of isonicotinyl hydrazine. Previous reports have shown that other hydrazone derivatives possessed an antituberculous activity corresponding to an equivalent dose of isoniazid, but that the pyruvate caused much less excretion of pyridoxine than isoniazid with consequently a lesser likelihood of peripheral neuritis. In a study at the Chelsea College of Science, London, the metabolism of isoniazid was compared with that of isoniazone calcium pyruvate in healthy subjects and in patients with pulmonary tuberculosis.

The excretion of free isoniazid and its derivatives was measured in 6 healthy subjects and in 6 tuberculous patients after a dose of 400 mg. isoniazid or its equivalent of 850 mg. isoniazone calcium pyruvate. This showed a lower excretion at 12 and 24 hours after the administration of pyruvate, primarily because of reduced excretion in the first 4 hours. The metabolic pattern of the two groups of subjects was the same.

Blood samples taken from the 6 tuberculous patients during the above investigation at 1½, 4½, 7, 12, and 24 hours showed a consistently lower isoniazid concentration at peak periods with the pyruvate—about one-half to one-third of that obtained with isoniazid, the peak being reached between 1 and 5 hours. The results suggested, however, that from 12 to 24 hours after administration the pyruvate would yield higher active levels. Similar results occurred after repeated dosage.

The effect on pyridoxine excretion was determined in healthy volunteers given daily doses of 16 mg. isoniazid per kg. and 34 mg. isoniazide calcium pyruvate per kg. Side-effects were severe, only 5 subjects completing the test, and no clear evidence was obtained that there was a lower pyridoxine excretion with the pyruvate. Differences found in slow and rapid inactivators are discussed. *B. Golberg*

960. Home Treatment of Tuberculosis in the Nyeri District of Kenya

P. P. TURNER. *Tubercle [Tubercle (Lond.)]* 43, 76-82, March [received May], 1962. -3 figs., 36 refs.

Between 1956 and 1958 a scheme of home treatment for patients with tuberculosis was tried in the Nyeri district of Kenya, a hilly, wooded area of 322 sq. miles (834 sq. km.) populated entirely by the Kikuyu, and the results are assessed in this paper from Coast Province General Hospital, Mombasa. A census in 1956 showed that the population numbered 217,000 and that there were, on the average, 5.2 persons in each hut, which in most instances consisted of one room. The inhabitants were grouped in 169 villages, the largest of which had a population of 3,800. During the 2-year period 821 cases of pulmonary tuberculosis were registered; the incidence in the age group 7 to 15 years was twice as high in females as in males. All patients presenting themselves were treated without selection, for the most part as out-patients. A minority who were very ill were treated in hospital "for a few weeks" until they were able to continue as out-patients. In all cases sputum smears and chest radiographs were examined, the erythrocyte sedimentation rate was determined, and weight recorded.

At the first examination 68% of all patients had sputum positive for tubercle bacilli on direct smear. Primary tuberculosis was present in 183 (22%) of the 821 patients. In some children the diagnosis was established from the x-ray appearances of the chest and a positive Mantoux reaction (5 t.u.). Following an "indoctrinary talk" with a member of the hospital staff the patients selected one of 14 centres in the district at which to attend for treatment. Each of these centres was visited by the author and his staff once a month.

Treatment for adults consisted in administration of 150 mg. of isoniazid and 5 g. of *p*-aminosalicylic acid (PAS) twice daily for 18 months, smaller doses being given to children. District health assistants working in the field ensured that the patients attended the centres regularly (a 90% attendance was usual) and collected fresh supplies of drugs. Few patients obeyed the instruction to rest. Every 3 months the condition of the patients was reassessed by the same procedure as at the initial examination. Occasionally urine was tested for PAS to determine whether the drug was being taken. It was considered that 85% of the patients were carrying out the treatment. Only 8% admitted difficulty in taking PAS.

Of the 821 patients 62 (7.5%) died, the mortality being the same in both sexes; half of these deaths occurred within a month of starting treatment. A total of 65 patients were lost to follow-up and 29 moved away to other districts. At the end of 18 months 221 patients were reviewed. Thin-walled persistent cavities were often seen. Sputum culture, facilities for which were limited, was carried out in 20 patients who had a "smear-negative sputum" at 6 months and 20 who were similarly negative at 12 months; positive results

were obtained in only 2 cases in each group. [The author does not state how many specimens were cultured from each patient—seemingly only one.] There were few toxic effects; pellagra was seen in 2 cases but no severe reactions to PAS were encountered.

The incidence of pulmonary tuberculosis at the end of the 2 years was 3.78 per 1,000. The author states that it varied greatly from village to village, being as low as 1.7 per 1,000 in one village and as high as 12.1 per 1,000 in another. The size of the village was the only environmental factor which appeared to be related to this difference. The coefficient of correlation with village population was +0.62 with a standard error of 0.28.

[This is an interesting, if somewhat frustrating, study. The number of patients satisfactorily followed up whose sputum was free from tubercle bacilli is not stated. Technical difficulties in the field (especially if the climate is tropical) are, of course, great, but even so it is limiting to have to rely mainly upon direct sputum smears, and lack of information about drug sensitivity or resistance of organisms is a great disadvantage. Again, no data are given about the changes in the chest radiographs with treatment. In Ghana, Bell found a high rate of bacillary resistance to the standard antituberculous drugs in patients apparently not previously treated, as well as in those who had received treatment. While understanding the difficulties confronting the present author the abstractor cannot help wondering to what extent the rather low isoniazid-PAS dosage (which may not have been taken quite as assiduously as appeared) may be contributing to the insidiously rising global store of drug-resistant tubercle bacilli.] *W. Raymond Parkes*

961. Adrenal Cortical Function in Chronic Pulmonary Tuberculosis

T. UETE. *British Journal of Diseases of the Chest [Brit. J. Dis. Chest]* 56, 87-95, April, 1962. 26 refs.

Writing from Gifu University, Japan, the author reports the results of an investigation of the adrenocortical function of 34 tuberculous patients. There were 25 males and 9 females in the series, and their ages ranged from 19 to 47 years, the majority being between 20 and 30. The 24-hour excretion of both conjugated and unconjugated 17-hydroxycorticosteroids was measured and the proportion of the 2 fractions calculated. The results were compared with those obtained in a normal control series of 50 males and 45 females. In the 13 patients with minimal tuberculous lesions the urinary excretion was normal. In 4 of 10 cases with moderately advanced lesions the total content of 17-hydroxycorticosteroids in the urine was low, because of reduction in the conjugated fraction. Of the 11 patients with advanced disease, 9 excreted an abnormally low amount of 17-hydroxycorticosteroids; of these, 4 showed a decrease in the conjugated fraction and 5 had low values for both fractions. Some correlation was established between lowered excretion of 17-hydroxycorticosteroids and the course of the disease; most of the cases returning low values were febrile and had a raised erythrocyte sedimentation rate, tubercle bacilli in the sputum, and progressive disease. The conclusion is that patients with moderately advanced and advanced pulmonary tuberculosis have a form of adrenal insufficiency.

The significance of the findings is discussed.

H. F. Reichenfeld

Venereal Diseases

962. **The Oculo-urethro-synovial Syndrome of Reiter, a Nosological Entity.** (With Reference to 117 Cases.) (Le syndrome oculo-urétré-synovial de Fiessinger-Leroy-Reiter, une entité nosologique. (A propos de 117 observations)) H. FÉLIX, P. CANAL, N. DUPRÉ, C. OURYUX, and A. GASCARD. *Journal de médecine de Lyon [J. Méd. Lyon]* 43, 671-690, April 20, 1962. 1 fig., 18 refs.

The authors recall that the disease generally known as Reiter's syndrome was described by Fiessinger and Leroy in 1916, the same year in which it was reported by Reiter. They describe here the clinical features in 117 patients who had contracted the disease in Algeria and whom the authors saw at the Desgenettes Military Hospital, Lyons. The onset was always during the hot summer or autumn months and was associated with enteritis in 95% of cases. The intestinal infection was thought to be due to an enterovirus which has not yet been isolated. War conditions favoured the outbreak of epidemics of this disease. In the present series there were few severe cases and the immediate prognosis was good, but, the authors point out, because of the possibility of ankylosing spondylitis developing later the long-term prognosis should be guarded. There is no specific treatment, but corticotrophin was found to shorten the duration of the painful arthritic stage. G. W. Csonka

963. **Sensitivity Tests as a Means of Distinguishing Relapse from Re-infection in the Treatment of Gonorrhoea** H. C. GJESSING and K. ØDEGAARD. *British Journal of Venereal Diseases [Brit. J. vener. Dis.]* 38, 26-29, March [received May], 1962. 3 refs.

The length of the interval between apparent cure and the reappearance of a discharge, and the presence or absence of a history of fresh exposure, are elements which help to distinguish between gonococcal re-infection and relapse. A short interval and absence of exposure are in favour of relapse, a longer interval and renewed exposure suggest re-infection. The distinction may also be made easier by a change in the penicillin sensitivity of the gonococci.

By brief accounts of 4 cases the authors, writing from the State Institute of Public Health, Oslo, illustrate four different sensitivity patterns. The method of gonococcal culture used, a plate dilution sensitivity test with 1 to 0.0075 unit of penicillin per ml., and a paper disk sensitivity test, are described. The drugs used in the paper disk method were penicillin, streptomycin, tetracycline, chloramphenicol, and a sulphonamide. The sensitivity pattern of gonococci isolated on first attendance is compared with that found after relapse or recurrence. The terms resistance and sensitivity are used in a relative sense, different degrees of resistance and sensitivity being expressed as I to IV. A significant difference in the sensitivity pattern (at least 3 degrees in the dilution scale are desirable) between first and second isolation of gonococci is in favour of re-infection. There may be resistance on first isolation and sensitivity on second isolation or vice versa. Sensitivity on both occasions may mean either re-infection or relapse, whereas resistance on both occasions is in favour of relapse. F. Hillman

SYPHILIS

964. **Oral Erythromycin in the Treatment of Early Syphilis** M. B. MOORE JR., E. M. VANDERSTOEP, J. M. KNOX, and C. H. MONTGOMERY. *Journal of Investigative Dermatology [J. Invest. Derm.]* 38, 285-288, May, 1962. 5 refs.

In this paper are summarized the results obtained at the Social Hygiene Clinic, Houston, Texas, in 130 dark-field positive cases of primary and secondary syphilis treated orally with erythromycin propionate. Three schedules of treatment were used: (1) 250 mg. 4 times daily for 10 days—a total of 10 g. (35 cases); (2) 500 mg. 4 times daily for 10 days—a total of 20 g. (34 cases); and (3) 500 mg. 3 times daily for 10 days—a total of 15 g. (61 cases). The failure rates were as follows:

Treatment Schedule	Followed 6 Months or Longer			Followed 9 Months or Longer		
	Total Cases	Failures	%	Total Cases	Failures	%
1 (35 cases)	21	3	14	14	3	21
2 (34 cases)	21	2	10	15	2	13
3 (61 cases)	24	1	4	13	1	8

It is considered that Schedule 3 (15 g. of erythromycin propionate) gave as good results as Schedule 2 (20 g.) and that either plan should prove satisfactory in the treatment of early syphilis. R. R. Willcox.

965. **Quantitative Studies on the Fixation Ratio "Complement:Antibody" in Complement-fixation Tests with Syphilitic Serum** H. G. S. RUGE. *British Journal of Venereal Diseases [Brit. J. vener. Dis.]* 38, 33-36, March [received May], 1962. 1 fig., 14 refs.

This paper from Kiel University is a further contribution to the author's previous studies in which he demonstrated that the fixation ratio between antibody and complement depends on the law of mass action. He has now been able to study the fixation ratio antibody:complement for both antilipoidal and antitreponemal antibodies.

The sera used were taken from known syphilitics and were stored at +4° C. Heterophil antibodies were removed by sheep-cell absorption, and antilipoidal antibodies by V.D.R.L. antigen absorption. Antitreponemal antibody absorption consumed too much treponemal suspension and was therefore discontinued. The test sera were diluted from 1:2.5 to 1:640 in several rows. For the cardiolipin complement fixation the front row received one haemolysis-producing unit of complement, and the next rows 2, 4, 8 "units", that is, 2, 3, 4 log. units. For the pallida reaction the amount of complement added to the different rows is expressed as a percentage, ranging from 10 to 20. Sera tested with cardiolipin numbered 20; 18 of them were tested

with *pallida* antigen (a) without absorption and (b) after absorption with V.D.R.L. antigen. The results of these tests are presented in tables and a diagram, in which the calculated and the observed results are compared. The calculation was by the method of least squares. The evaluation of the cardiolipin end-titres did not require more than 5 (1+4) "log. units" of complement (maximum titre 1:640++), whereas the *pallida* end-titres did not reach zero until 6 (1+5) "25% units" were consumed (maximum titre 1:640++). On the basis of these results an equation was prepared, reading, for example, for the cardiolipin test: y (log. complement) = $4.43 - 2.23 \times (\log. \text{antibody})$. The results demonstrate the dependence of the complement-fixation tests for syphilis on the law of mass action. The fixation-ratio antibody:complement in all experiments was 2:1; in other words, 2 parts of antibody, both antilipoidal and antitreponemal, are bound by one part of complement.

F. Hillman.

966. 617 Cases of Late Visceral Syphilis Observed in the Last 15 Years at the Regional Hospital Centre, Lille. (A propos de 617 cas de syphilis viscérales tardives recueillis ces quinze dernières années au C. H. R. de Lille) C. HURIEZ, P. AGACHE, and F. SOUILLIART. *Bulletins et mémoires de la Société médicale des hôpitaux de Paris* [Bull. Soc. méd. Hôp. Paris] 113, 466-476, 1962.

Tertiary syphilis is still an important problem in the north of France. This is thought to be the result of inadequate treatment during the epidemic of the disease which occurred during the war of 1914-18. The authors, working at the Clinic of Dermatology and Syphilology, Lille, have studied 617 cases of late tertiary syphilis—444 affecting the nervous system, 96 the aorta, and 77 the eyeball—treated at the Lille hospitals since 1945. In only 12% could a history of primary or secondary manifestations be established. The number of cases of tertiary syphilis detected annually in the district at the time of the report (March, 1962) was 27, or some 25% of what it was 20 years before. The proportion of cases due to neurosyphilis has greatly increased. In the group of general paralysis of the insane, forms with dementia or megalomania are less frequent, those with depression or confusion more frequent. The proportion of cases of cerebrovascular syphilis, of syphilis of the spinal cord, and cardiovascular syphilis with aneurysm or aortitis, has fallen. The number of cases with positive serological evidence of syphilis but relatively little clinical evidence is now much higher. In the series considered here the treponemal immobilization (T.P.I.) test was positive in all but 2 patients (one with tabes who had received prolonged treatment and one with general paralysis who had had malaria therapy).

As regards treatment the authors favour the use of mercuric cyanide and bismuth in addition to penicillin. They cite 12 patients in whom treatment with penicillin, sometimes in high dosage, was given during the second year of the infection, but who later developed tertiary manifestations. Of the 617 cases, 27% had 10 million units of penicillin, 35% had 11 to 30 million units, 30% had 31 to 100 million units, 9% had over 100 million units, and 283 had mercuric cyanide or bismuth in addition to penicillin. Pyretotherapy, in association with chemotherapy or metals, was used in 93 cases of syphilis of the nervous system. In tabes there was little improvement in symptoms due to sclerotic or degenerative lesions, but improvement did occur in lightning pains,

visceral crises, and ataxia. In general paralysis, the mental state improved in 56%; 40% of the patients in mental hospitals could be discharged, and 64% of those treated outside were able to resume their work. The results in cardiovascular syphilis were less favourable, but improvement was obtained in over 50% of the cases of anginal attacks and precordial pain. Only 17% of cases of cardiac dysrhythmia and 8% of cases of dyspnoea improved. In interstitial keratitis, better results were obtained than previously by giving local treatment with corticosteroids in addition to general treatment with penicillin and mercuric cyanide. In none of the cases did the T.P.I. test become negative. Pleocytosis in the cerebrospinal fluid was markedly reduced by treatment; the higher it was to begin with, the greater was the reduction. There were 5 Herxheimer reactions after penicillin, 4 of them fatal. The authors consider that previous administration of mercuric cyanide and of prednisone would reduce the incidence of this complication.

Among the 93 patients who had pyretotherapy there were 7 deaths.

J. A. Farfor

967. Tabetic Arthropathy in Rheumatology. (L'arthropathie tabétique en rhumatologie) S. DE SÈZE, A. HUBAULT, and J. C. CHANUT. *Bulletins et mémoires de la Société médicale des hôpitaux de Paris* [Bull. Soc. méd. Hôp. Paris] 113, 444-450, 1962. 6 figs.

The authors report a detailed scrutiny of 29 cases of tabetic arthropathy seen in the department of rheumatology of a Paris hospital since 1950. In 12 of the cases, at least 4 of the following clinical features of tabes were present: abolition of tendon reflexes, ataxia and Rombergism, Argyll Robertson pupil, disturbance of deep sensation, lightning pains, visceral crises. In 15 cases at least 2 of these features were present. In one case only was the osteoarthropathy the sole objective sign of the disease. [No serological investigations are reported.] In all the cases the presence of tabes had been unsuspected and was discovered only on examination at the rheumatology centre. In 15 of the cases multiple joint involvement supported the view of Foix and Alajouanine that arthropathy occurs in tabetics who have a predisposition to joint disease. The two striking points which emerged from the study are: (a) that pain does occur in tabetic arthropathy, and (b) that the differential diagnosis between tabetic arthropathy and osteoarthritis may be difficult. In 18 of the cases the tabetic arthropathy was situated in the knee, and in 11 of these it was on account of pain that the patients attended. The pain had been present for, on an average, 3 to 5 years, and had generally been subject to remissions. The vertebral column was affected in 8 of the 29 cases.

Arthropathy is a relatively rare feature of tabes (5 to 10% of cases). Osteoarthritis, on the other hand, is a common disease, and may well occur in tabetic subjects. The differential diagnosis may be especially difficult in atypical cases of tabetic arthropathy, in which pain is a marked feature, while other clinical evidence of tabes is lacking. The mode of onset, and the presence or absence of joint deformity and of stiffness and limitation of movement, are criteria of doubtful value. Of greatest help are (a) the x-ray appearances, and (b) the mode of evolution. In tabetic arthropathy the characteristic radiological finding is condensing osteolysis with ill-defined limits, while the evolution of the disease is much more rapid than that of osteoarthritis.

J. A. Farfor

Tropical Medicine

968. **A Further Clinical Contribution to the Study of Acquired Toxoplasmosis of the Adult.** (Ulteriore contributo clinico alla toxoplasmosi acquisita dell'adulto)

I. V. TONDI, C. FERRARI, and C. FILOGRANA. *Riforma medica* [Rif. med.] 76, 677-682, June 23, 1962. 13 refs.

The authors, writing from the University of Messina, state that the 2 cases of toxoplasmosis they previously described were regarded as unusual in their part of the world, but that the 4 further cases which have come to their notice within a year force them to conclude that the disease is endemic in the province of Lecce (Southern Italy).

The 4 new cases, all in adults, one aged 71 and the others between 20 and 24 years, are described in detail. In 2 the disease ran a subchronic course; one of these was a young woman who had had symptoms for 7 years, had undergone a number of gynaecological operations, and had twice been regarded as suffering from typhoid fever. In the other 2 patients the condition was acute. In one of the patients elements regarded as toxoplasma were found in the centrifuged cerebrospinal fluid. In 3 patients intradermal tests with toxoplasmin were strongly positive and in 3 the Sabin-Feldman dye test was strongly positive. The results of complement fixation tests were negative in the 2 patients in whom the tests were performed. In 3 cases the disease seemed to begin with convulsive movements, often tonic-clonic, in the limbs, and 3 had a morbilliform-scarlatinal rash. The young woman with a history of symptoms for 7 years had had paroxysmal headaches throughout that period. Radiography of the skull showed small calcified foci in her case, but nothing abnormal in the other 3 patients. Onset with convulsions, headache, and dulling of the mental processes suggests a diagnosis of cerebral tumour [although fundal changes were minimal in all], but the positive dye test and the rash point to a toxoplasmic encephalomeningitis, which may simulate a pseudo-rickettsiosis. Treatment was with sulphamethoxypyridazine and pyrimethamine. All 4 cases showed very considerable renal impairment in the acute stages but all apparently recovered completely. In a postscript the authors state that a further case had just come to their notice, that of a woman with a 10-year history of recurrent fever with headache and vomiting, in whom the dye test and the intradermal toxoplasmin test were strongly positive.

W. K. Dunscombe

969. **Treatment of *Schistosoma haematobium* Infection with Sodium Antimony Dimercaptosuccinate (TWSb)**

H. F. NAGATY, M. A. RIFAAT, H. M. KHALIL, and T. A. MORSE. *Journal of Tropical Medicine and Hygiene* [J. trop. Med. Hyg.] 65, 91-94, April, 1962. 11 refs.

In this paper from Ein Shams University, Cairo, a trial is reported of sodium antimony dimercaptosuccinate (TWSb) in the treatment of infection due to *Schistosoma haematobium*. A group of 117 school-children were given three intramuscular injections of 0.25 to 0.3 g. of TWSb at monthly intervals. The sediment in the urine from 72 of the children contained ova of *S. haematobium* before treatment; urine from the remaining children was free from ova.

Some of the children vomited 2 to 3 hours after the injection and in 3 syncope occurred. The absentee rate increased after the first injection and only 39 of the children received the full course of three injections. With this treatment the number of ova passed in the urine decreased but the effect was not permanent; 2 months after the last injection all the children were passing ova in the urine.

When 5 doses each of 0.3 to 0.4 g. were given at weekly intervals to 40 patients aged 10 to 45 years the results were much better. Vomiting, lassitude, and generalized aches occurred but did not warrant curtailment of the treatment. In all cases the urine was free from ova 15 days after the fifth injection. There was a relapse in one of the 40 patients after 2 months, and in one out of 3 examined after 6 months. A further 25 patients were given 5 injections of 0.3 to 0.4 g. with varying intervals between the doses; most of them received the drug at fortnightly intervals. The urine in all except one of the patients was free from ova 2 months after the start of treatment. The authors point out that administration of TWSb at intervals of 10 to 15 days enables mobile units to move freely from village to village and allows patients to go back to work between injections.

L. G. Goodwin

970. **Clinical Observations on 110 Cases of *Ascaris* Invasion into the Biliary Tract**

FU-HSING HSU. *Nagoya Journal of Medical Science* [Nagoya J. med. Sci.] 24, 215-233, March, 1962. 3 figs., 44 refs.

Invasion of the biliary tract by *Ascaris lumbricoides* is a relatively common condition in Japan; it is seen in about one-third of all patients operated on for biliary disease. Accurate clinical diagnosis is possible in the majority of cases (over 70%) provided the syndrome is borne in mind.

In this paper the author describes 110 cases operated on at the Kao-Hsiung Hsu Surgical Clinic, Japan, between August, 1955, and January, 1961. The symptoms were somewhat similar to those of cholelithiasis, which seemed to be a precipitating factor in some of the cases. Most, but not all, of the patients had a history of vomiting *Ascarides* or passing them per anum. The majority of the patients when admitted to hospital had a severe colicky pain primarily in the epigastrium (with the most severe pain just below the xiphisternum), but the pain radiated in various directions, radiation towards the back being the most common. Of the 110 patients 33 had fever and 90 complained of nausea and vomiting. A few were semicomatose on admission, apparently due to the pain. Jaundice was rare. The condition was found in patients of all ages but was most common in the age group 30 to 40 years, and was seen 4 times more frequently in females than in males.

Choledochotomy was carried out in all the cases with, in one case, cholecystectomy. In 105 cases, at least part of the worm was in the common bile duct; in the remaining cases the hepatic duct or gall-bladder was involved. One worm only was present in 92 cases; more than 3 worms were rarely seen. The choledochus was enlarged in 52 patients and the gall-bladder in 24.

W. H. Horner Andrews

Allergy

971. Treatment of Allergy with Oral Betamethasone in 141 Patients

A. I. COHEN. *Antibiotics and Chemotherapy [Antibiot. and Chemother.]* 12, 91-96, Feb. [received May], 1962. 14 refs.

Betamethasone, in which the methyl radical is attached at the 16- β position instead of the 16- α position, is the most active of the synthetic corticosteroids available, being eight times more potent than prednisone. The drug was given to 141 patients with respiratory or skin diseases of allergic origin in a dosage of 1.8 or 2.4 mg. daily, which was reduced after 3 days to 0.6 or 1.2 mg. daily. Children received a proportionate dosage according to weight, usually 0.6 mg. daily. Treatment was given for 3 to 29 days, mean 14 days. The response to treatment was rapid; in 97% of the patients there was satisfactory relief of symptoms within a week. The treatment failed in 2 cases and 3 patients preferred prednisolone. The incidence of side-effects (3%) was very low. A. W. Frankland

972. Allergy to Insect Emanations, Clinical Importance. Some Immunological and Therapeutic Aspects. (Allergie aux émanations d'insectes, importance clinique. Quelques aspects immunologiques et thérapeutiques)

C. BENAÏM-PINTO. *Acta allergologica [Acta allerg. (Kbh.)]* 17, 74-85, 1962. 9 refs.

Skin tests to insects gave positive results in 135 (67.5%) of 200 cases of respiratory allergy investigated at the Hospital Municipal J. M. de los Ríos, Caracas, Venezuela. The allergic manifestations were rhinitis in 105 cases, asthma in 102, atopic dermatitis in 9, urticaria in 8, acute conjunctivitis in 5, migraine in 5, hypersensitivity to insect bites in one, and anaphylactoid purpura in one. Of the 135 patients 103 reacted positively to more than 50% of the species of insect used for testing, 120 (88.8%) also reacted to house dust, and only 3 reacted to insects only. Of the 65 cases which reacted negatively to insects, only 42 (64.9%) reacted positively to house dust. Neutralization tests showed that common antigens exist among the insects, but the author recommends that, for the treatment of patients hypersensitive to bees, wasps, and ants, all the individual species should be used. G. B. West

973. The Prophylaxis of Allergic Disease in Infancy

J. GLASER. *Pediatrics [Pediatrics]* 29, 835-842, May, 1962. 29 refs.

After reviewing the question of the prophylaxis of allergic disease in infants and referring to the importance of cow's milk and raw egg yolk as causes of allergic disturbances in infancy, the author, writing from the University of Rochester, New York, reports a detailed study of over 300 potentially allergic children. About 4 times as many infants in a control group developed atopic dermatitis as compared with an experimental group in which cow's milk was withheld from birth and the majority of the infants were given soya-bean milk. In the author's experience, some 50% of the infants who suffer from atopic dermatitis eventually develop asthma. He draws attention to the importance of differen-

tial diagnosis between atopic dermatitis, which is an allergic disease, and seborrhoeic dermatitis, which is not. There is evidence that "cot-death"—that is, the death of an infant during sleep without apparent adequate cause—may be due to potential or actual sensitization to cow's milk, inhalation of regurgitated stomach contents into the tracheo-bronchial tree leading to an anaphylactic reaction. So-called "eczema deaths", which became less frequent when evaporated milk was introduced for routine infant feeding instead of pasteurized whole cow's milk, are perhaps caused in the same way. (Evaporated milk is said to be less allergenic than whole cow's milk.) The author believes that for the prophylaxis of allergic disease, human breast milk is the ideal food for the newborn infant, but that if the trend away from breast feeding cannot be reversed, then a well-tolerated substitute, such as soya-bean milk, is preferable to cow's milk. A satisfactory preparation of soya-bean milk may be made at home inexpensively from soya-bean flour. G. B. West

974. Effect of Repository Therapy on Immunological Responses to Pollen Extract

H. FRIEDMAN and L. H. CRIEP. *Journal of Allergy [J. Allergy]* 33, 215-231, May-June, 1962. 6 figs., 39 refs.

Single repository injections of pollen extract in an emulsion containing mineral oil were given to 110 ragweed-sensitive hay-fever patients who had been previously treated with aqueous pollen extracts, and 13 others who had never had any treatment. The emulsion contained 1,500 to 10,000 protein-nitrogen units per ml., according to the outcome of skin testing. In addition 8 non-allergic subjects were given a similar injection, 3 ragweed-sensitive patients received a placebo injection, and 347 ragweed-sensitive hay-fever patients were treated, as in previous years, with aqueous pollen extracts.

The haemagglutination titres, measured by the bis-diazotized benzidine method, increased in both patients treated with emulsion and those given aqueous extract, and blocking antibody titres likewise increased. Skin-sensitizing antibody titres and the results of complement-fixation and precipitin tests did not change. The degree of clinical relief did not correlate with any of the immunological changes, and marked or moderate relief occurred in 40 to 50% of the patients in both groups.

[An assessment of the clinical relief obtainable in a large group treated with placebo would be interesting.]

H. Herxheimer

975. Immediate Skin Reactivity Induced in Atopic and Nonatopic Persons following Injection of Emulsified Pollen Extracts: Clinical, Immunologic, and Serum Studies

D. B. SPARKS, S. M. FEINBERG, and R. J. BECKER. *Journal of Allergy [J. Allergy]* 33, 245-249, May-June, 1962. 5 refs.

In an investigation at Northwestern University Medical School, Chicago, 12 atopic and 8 non-atopic subjects received one depot injection of 10,000 units of either ragweed or timothy pollen extract, or both, in a mineral-oil emulsion. They were tested intradermally at weekly intervals. After

4 weeks 7 subjects had developed a positive immediate skin reaction, and after 8½ months 9 others had the same reactions, some of these showing also the delayed type of skin reactivity. Of the 8 non-atopic subjects, 3 did not develop skin reactivity. Serum from 4 out of 5 sensitized subjects gave a positive Prausnitz-Küstner reaction with non-allergic skin. The serum factor responsible for this was heat-labile and persisted at the skin site for at least 2 weeks. It is concluded that the emulsified antigen is a much stronger antigenic stimulus than antigen in aqueous solution, which does not sensitize non-atopic subjects. *H. Herxheimer*

976. Suppression of Asthma, Weight Gain, and Linear Growth in Children Receiving Fluprednisolone

E. P. DECANAY and T. E. VAN METRE JR. *Journal of Allergy [J. Allergy]* 33, 259-270, May-June, 1962. 5 figs., 16 refs.

At the Johns Hopkins Hospital, Bethesda, Maryland, 45 children aged 0 to 16 years and suffering from bronchial asthma were treated with fluprednisolone (6α-fluoroprednisolone), the corticosteroid potency of which is roughly equivalent to that of dexamethasone. Only 6 children received the substance for 6 months or longer. In these 6 cases linear growth appeared to be retarded, as had also been noticed previously with prednisone and methylprednisolone, but not with cortisone. Gain in weight was similarly affected, but cortisone in this case did not form a clear exception. Asthma was adequately controlled by fluprednisolone.

[It seems premature to draw conclusions from 6 cases, particularly as there was no suppression of weight gain in 2 of them. Besides, retardation of development is well known in children with severe asthma, and, as usually only such cases will receive corticoids, the primary disease must be considered as the cause of suppression of growth.]

H. Herxheimer

977. Effect of Cyproheptadine on Asthmatic Children: Study of Appetite, Weight Gain, and Linear Growth

A. F. LAVENSTEIN, E. P. DACANEY, L. LASAGNA, and T. E. VAN METRE. *Journal of the American Medical Association [J. Amer. med. Ass.]* 180, 912-916, June 16, 1962. 3 figs., 7 refs.

A double-blind comparative study is reported of the effect of cyproheptadine, an antagonist of histamine and serotonin, and that of chlorpheniramine on weight gain and linear growth in 28 asthmatic children seen at Johns Hopkins Hospital, Baltimore. It had been observed in a previous study that in patients given cyproheptadine there was a marked increase in appetite with an associated gain in weight.

The drugs were allocated to the children in a random manner and treatment was given for approximately 6 months. The average daily dosage per square metre of body surface was 18.5 mg. of cyproheptadine and 16.5 mg. of chlorpheniramine. Weight and height were measured at each attendance. At the end of treatment the 14 children given cyproheptadine showed a mean increase in weight of 284% [given in a table as 248%] of the expected normal and a mean increase in height of 133%. In the children given chlorpheniramine the respective figures were 123% and 99%. In all except one of the children receiving cyproheptadine there was a considerable increase in weight above the expected-normal and in 10 there was a rather less striking increase in height. No evidence of Cushing's syndrome or

hypothyroidism was found during the period of weight gain. Of the 14 patients given cyproheptadine 12 reported an increase in appetite compared with 3 of the 14 given chlorpheniramine. These observations and the accompanying increase in linear growth suggested that the weight gain was exogenous in type. Cessation of cyproheptadine therapy was followed by a decrease in appetite in 12 patients, a reduction in the rate of weight gain in 4, and an actual loss of weight in 8 patients. One patient in this treatment group maintained an accelerated weight gain and one was lost to follow-up.

In a previous study it was found that cyproheptadine and chlorpheniramine were equally effective in the treatment of hay-fever, and in the present investigation no difference was observed between them in their effect on asthma.

R. S. Bruce Pearson

978. Clinical Evaluation of a New Triple Drug Aerosol for Asthma

A. A. GOLDFARB and A. ROMANOFF. *Annals of Allergy [Ann. Allergy]* 20, 307-314, May, 1962. 1 fig., 5 refs.

A combination of isoetharine (*n*-isopropylethylnoradrenaline) with phenylephrine and the antihistamine thenyldiamine was tried as a bronchodilator aerosol in 76 patients suffering from asthma at the Lebanon Hospital, Bronx, New York. All the patients showed an increased timed vital capacity (T.V.C.) within 7 to 10 minutes of spraying with the triple compound, and 63 also had subjective relief from dyspnoea. The authors state that when the 3 constituents were tested singly and in combinations of 2 and of 3 in a double-blind study, the triple compound was superior to its single constituents and to their other combinations. [The authors' figures of increase in T.V.C. do not seem to justify this conclusion entirely.] One second after inhalation the average increase in T.V.C. with 0.6% isoetharine alone was 261 ml., with 0.6% isoetharine and 0.05% thenyldiamine 228 ml., with 0.6% isoetharine and 0.125% phenylephrine 208 ml., and with all 3 substances together 315 ml. The average increase in T.V.C. 3 seconds after inhalation was 194 ml. with isoetharine alone, 116 ml. with isoetharine and thenyldiamine, 175 ml. with isoetharine and phenylephrine, and 208 ml. with the triple compound. [The authors do not discuss why isoetharine with either of the other substances is weaker than isoetharine alone; nor do they give any statistical treatment of their results. This encourages scepticism towards claims for "synergism" in compound medicines.]

H. Herxheimer

979. Methandienone in Long-term Corticosteroid Therapy

R. G. EVANS. *Acta Allergologica [Acta allerg. (Kbh.)]* 17, 220-231, 1962. 3 figs., 6 refs.

Many anabolic agents appear to have virilizing side-effects and some can be given only by injection. At the General Hospital, Nottingham, methandienone was given in a dosage of 0.1 to 0.25 mg. per kg. body weight to 20 asthmatic patients who were receiving long-term corticosteroid therapy. No virilizing or hepatotoxic side-effects were observed with this dosage, and there was no evidence of salt retention. Moreover, chronic protein loss was reduced or corrected and growth in children was stimulated. Radiological improvement in osteoporosis was observed after 6 months and in 2 cases there was dramatic relief from referred dorsal pain within 10 to 12 days.

A. W. Frankland

Nutrition and Metabolism

980. Scurvy and Anaemia

E. V. COX, M. J. MEYNELL, W. T. COOKE, and R. GADDIE. *American Journal of Medicine* [Amer. J. Med.] 32, 240-250, Feb., 1962. 4 figs., bibliography.

Scurvy developed in 7 adults on self-imposed diets, consisting mainly of bread, butter or margarine, and tea, taken for 7½ months to 15 years. One patient had pernicious anaemia, 2 had a normal blood picture (Group 1), and 4 had a normocytic hypochromic anaemia and macronormoblastic marrow (Group 2). The leucocyte and differential counts were normal in all cases; the platelet count was low in 2 patients in Group 2. Treatment with ascorbic acid at the General Hospital, Birmingham (England), cured the scurvy in all patients, but caused complete haematological remission in only 2 patients, both in Group 2.

Serum albumin concentration was low in all Group-2 patients; serum calcium and iron levels were also low in 2 of them. The serum level of seromucoids was raised in all patients in Groups 1 and 2. Ascorbic acid (250 mg.) injected intravenously was cleared more rapidly from the blood of all scorbutic patients than from controls, the blood level being less than 0.5 mg. per 100 ml. in 45 minutes.

In 2 patients in Group 1 and all those in Group 2, treatment with ascorbic acid resulted in a decreased urinary excretion of folic acid when this was given orally or intramuscularly, with no significant change in the amount of citrovorum factor. It is suggested that these findings indicate an association between ascorbic acid and the pteroyl-glutamate complex.

M. Lubran

981. Hydroxocobalamin, Natural Long-acting Vitamin B₁₂. (L'hydroxocobalamine, vitamine B₁₂ retard naturelle)

B. SUREAU, J. BERROD, L. MARTIN, and L. FOISIL. *Presse médicale* [Presse méd.] 70, 1388-1390, June 9, 1962. 8 refs.

The present state of knowledge of the action of hydroxocobalamin (vitamin B_{12b}) is briefly reviewed. Results are quoted to show that this substance maintains a higher blood level than cyanocobalamin over a longer period, and that it is more slowly excreted in the urine. These results were obtained with single intramuscular doses of 1,000 µg. The difference in rate of excretion of the two cobalamins was apparent after intramuscular administration only, and not after intravenous administration. The more prolonged action of hydroxocobalamin is considered to be due partly to slower absorption from the injection site and slower excretion in the urine and partly to non-specific combination with the proteins of the serum, especially α₁- and α₂-globulins, and of the tissues. It is as effective as cyanocobalamin but can be given less frequently and in lower dosage. The liver fixation ratio of hydroxocobalamin:cyanocobalamin has been found to be 1.5:1, and the retention ratio 2.7:1 for doses of 500 µg. and 3.1:1 for doses of 1,000 µg. A dose of 1,000 µg. of hydroxocobalamin every 49 days is said to have the same effect as the same dose of cyanocobalamin every 16 days. The authors have used the preparations in a series of over 60 patients. [There is no indication of where the work was performed.] Patients are described who, with normal blood pictures, showed relief of anorexia,

general malaise, and depression on administration of 1,000-µg. doses of hydroxocobalamin daily for periods of up to 3 weeks.

F.W. Chattaway

982. Hypoglycaemia as a Cause of Convulsive Disorder

T. MCKENDRICK. *Developmental Medicine and Child Neurology* [Develop. Med. Child Neurol.] 4, 328-335, June, 1962. 4 figs., 14 refs.

The author of this paper from the Hospital for Sick Children, Great Ormond Street, London, briefly describes the causes, clinical features, and methods of diagnosis of hypoglycaemic convulsions in children. The organic causes include hyperinsulinism, enzymatic defects, and lesions of the anterior pituitary, adrenal glands, and hypothalamus. The functional causes include hyperinsulinism, leucine sensitivity, and several other unusual factors. Suspicion of the hypoglycaemic nature of the convulsions may be aroused if symptoms of adrenaline release precede the fits or they occur in the fasting state. Aids to diagnosis in all cases of unexplained convulsions are the blood sugar level, and, more specifically, the response to glucose, insulin, adrenaline, casein, tolbutamide, or fasting.

T. B. Begg

983. Effects of Anabolic Steroid, Methandienone, on Carbohydrate Metabolism in Man

J. LANDON, V. WYNN, J. N. C. COOKE, and A. KENNEDY. *Metabolism: Clinical and Experimental* [Metabolism] 11, 501-512, May, 1962. 46 refs.

The effect of anabolic steroid drugs on protein metabolism has been extensively studied. Their influence on carbohydrate metabolism, which has received little attention, was the object of this study reported from St. Mary's Hospital, London, and the Royal Air Force Hospital, Wroughton.

Methandienone was given to 8 healthy young men (controls) and, on various therapeutic grounds, to 25 patients (15 male and 10 female, aged 14 to 55 years) in a dosage of 0.8 mg. per kg. body weight daily for 14 to 28 days to the controls and 0.19 to 2.37 mg. per kg. daily for 7 to 483 days to patients.

The drug lowered the fasting blood sugar level to a highly significant degree in both controls and patients, but the level did not fall below 60 mg. per 100 ml. The fall was negligible if the fasting blood sugar level was originally less than 80 mg. per 100 ml. A dose of more than 0.6 mg. per kg. (13 patients) produced a significantly greater fall than a smaller dose (12 patients). The response to the prednisolone-loaded glucose tolerance test was normal in all subjects, indicating that none was pre-diabetic. Methandienone produced a higher maximum blood sugar level and a delayed fall in 7 out of 8 healthy subjects and in 18 out of 23 patients after glucose administration. This effect was not related to the dosage of the drug, and it began within 7 to 9 days. The peak level was 180 mg. per 100 ml. (mean) in healthy subjects and 168 mg. per 100 ml. in the patients. Intravenous glucose tolerance tests before and during methandienone therapy showed that in 9 out of 11 patients the drug slowed the rate of removal of glucose from the blood; this did not depend upon the dosage and was noted within 14 days.

Fasting blood pyruvate levels in 14 patients were unchanged even by high and prolonged dosage of methandienone, and the blood pyruvate curves with oral and intravenous glucose loads were normal before and during methandienone therapy, except in one obese girl, in whom the drug accentuated an abnormality. The authors state that normal pyruvate curves favour normal glucose utilization. There may be impaired glucose uptake by the liver and a block in hepatic glycogenolysis. Methandienone certainly alters hepatic function, since it raised the serum levels of glutamic-oxalacetic transaminase, glutamic-pyruvic transaminase, and lactic acid dehydrogenase in some subjects and delayed "bromsulphalein" excretion in the majority.

T. B. Begg

984. Effects of Anabolic Steroid, Methandienone, on Carbohydrate Metabolism in Man. II. Effect of Methandienone on Response to Glucagon, Adrenalin, and Insulin in the Fasted Subject

J. LANDON, V. WYNN, B. J. HOUGHTON, and J. N. C. COOKE. *Metabolism: Clinical and Experimental [Metabolism]* 11, 513-523, May, 1962. 27 refs.

In this further paper on the influence of an anabolic steroid on carbohydrate metabolism (see Abstract 983), the authors report the effects of methandienone on the response of nondiabetic subjects to glucagon given intravenously, adrenaline given subcutaneously, and insulin given intravenously.

In all except one of the 31 subjects given glucagon intravenously the hyperglycaemia was reduced by more than 50% during methandienone therapy and the associated fall in the plasma inorganic phosphorus level was less than normal. These effects were more marked after prolonged treatment with methandienone; after 96 days the hyperglycaemic action of glucagon was almost completely blocked. However, the hyperglycaemic effect and the reduction in plasma inorganic phosphorus level induced by subcutaneous administration of adrenaline were not altered by methandienone (11 subjects). In 22 subjects given insulin intravenously there was no change in insulin sensitivity or, at the most, a slight resistance to insulin during treatment with methandienone.

In a discussion the authors point out that since methandienone inhibits the hyperglycaemic reaction after glucagon but does not alter that after adrenaline, the hepatic store of glycogen must be adequate and the glycogenolytic pathway intact. It is possible that liver phosphorylase can be converted from an inactive to an active form in two different ways and that methandienone blocks one such conversion.

T. B. Begg

985. Dietary Starch: Effect on Cholesterol Levels

D. R. FARNELL and M. J. BURNS. *Metabolism: Clinical and Experimental [Metabolism]* 11, 566-571, June, 1962. 20 refs.

Feeding experiments were carried out on rats at Auburn University, Alabama. The animals were kept on a cholesterol-free diet with identical fat content, but with either casein or soya bean as the protein source. Carbohydrate was supplied either as glucose alone or as a mixture of glucose and corn starch. After 3 weeks the animals were killed and the cholesterol content of serum and liver was determined. It was found that regardless of the protein source, animal or plant, the cholesterol content of the liver was

lower when starch had been part of the diet. In the rats fed on casein, starch was not found to affect the serum cholesterol level, but in the rats fed on soya-bean protein the serum cholesterol level was higher when they received starch in addition to glucose. The authors suggest that starch in some way makes available riboflavin, which may be required for the mobilization and subsequent breakdown of cholesterol to bile acids. Dietary starch would then lower liver cholesterol but may raise serum levels, probably by increasing the mobilization and excretion of cholesterol. The authors mention an interesting possible connexion between this work and the epidemiology of atherosclerosis. The lower incidence of atherosclerosis in Thailand than in Japan may be due to the fact that the Thai consume more carbohydrate, derived almost entirely from rice, than do the Japanese.

H. Lehmann

986. Multiple Precipitins to Cow's Milk in Chronic Respiratory Disease

D. C. HEINER, J. W. SEARS, and W. T. KNIKER. *American Journal of Diseases of Children [Amer. J. Dis. Child.]* 103, 634-654, May, 1962. 7 figs., bibliography.

The authors, at the County Hospital, Salt Lake City, Utah, examined the sera of 2,200 children for precipitins to cow's milk; they describe the clinical findings in 8 whose sera contained the greatest number of precipitins.

The precipitin tests were made by the technique of double diffusion in agar. The antigens were provided by pooled raw whole cow's milk, which was used undiluted, and special tests were made with purified fractions, beta-lactoglobulin, gamma-lactalbumin, and others. The sera were from centrifuged whole clotted blood, used undiluted.

Of the 2,200 patients, 8 had antibodies to 5 or more milk constituents as shown by the consistent development of 5 or more precipitate bands in agar. In these 8 children a striking association of symptoms and signs was observed, including chronic cough, tachypnoea, chronic rhinitis, recurrent fever, frequent earache, diarrhoea, vomiting, and haemoptysis. Examination revealed evidence of recurrent pneumonia, recurrent otitis media, poor growth, hypochromic anaemia, and eosinophilia. Intradermal skin testing gave a positive immediate reaction to one or more components of milk in all the patients. In 4 patients who had haemoptysis, the finding of iron-laden macrophages in bronchial or gastric aspirates indicated similarity of their illness to, or identity with, idiopathic pulmonary haemosiderosis. The age of onset of symptoms ranged from 13 days to 6 months; in 3 infants onset was during breast feeding. In 6 children treatment consisted in changing the milk content of the diet. In 2 a diet of evaporated milk abolished the symptoms, while in 4 this result was achieved only by a diet free of cow's milk; in 2 of these children symptoms returned when milk was given again. There was evidence of allergic illness in the families of 7 of the children, and siblings of 3 had died in early childhood (one found dead in her crib at the age of 12 months). The authors point out that the association of recurrent pulmonary disease and milk sensitivity has not been reported before.

Of the 2,200 patients whose sera were tested, 18 also had antibodies to certain milk constituents, but, unlike the 8 just described whose sera produced multiple and heavy precipitate bands, they did not constitute a group having a recognizable syndrome.

C. O. Carter

Gastroenterology

987. **Pancreatic Enzyme Replacement Therapy in Malabsorption of Pancreatic, Hepatic, and Gastric Origin**
F. STEIGMANN, D. SNYDER, and A. FERNANDEZ. *American Journal of Digestive Diseases* [Amer. J. dig. Dis.] 7, 464-472, May, 1962. 2 figs., 45 refs.

In this paper from the University of Illinois College of Medicine, Chicago, the authors, after classifying and discussing malabsorptive states, describe a study of pancreatic enzyme replacement therapy in malabsorption, using a new pancreatic concentrate, "cotazym". Of the 32 patients studied, 20 had pancreatic disease, 4 chronic hepatitis, 3 gall-bladder disease, 3 post-gastrectomy syndrome, and 2 non-specific bowel disease. All patients received a high-protein diet and all had specific treatment in addition to cotazym, the latter being given in the form of capsules, each containing 2,000 lipase units. Dosage was based on the amount of dietary fat, and some patients required over 6 capsules a day. The effect of cotazym on fat absorption was tested in 14 of the patients by means of triolein labelled with ¹³¹I. Patients with hepatitis were also given bile salts. The clinical progress of the patients was carefully checked.

Subjectively, all patients improved, there being a variety of reasons, such as less diarrhoea, a diminution of flatulence, and improved appetite. In 15 cases there was a gain in weight varying from 2 to 16 lb. (0.9 to 7.25 kg.) with an average of 8 lb. (3.6 kg.). The patients showing the greatest improvement were those with post-gastrectomy syndrome, 2 with chronic hepatitis, one with the bowel syndrome, and 3 with cystic fibrosis of the pancreas. There was greater variation in the amount of fat absorbed, but in many of the patients tested the enzyme concentrate produced a definite increase as compared with control values.

W. H. Horner Andrews

988. **The Early Diagnosis of Cancer of the Oral Cavity**
J. F. SMITH and D. H. SPRUNT. *Southern Medical Journal* [Sth. med. J. (B'ham, Ala.)] 55, 502-509, May, 1962. 16 figs.

Cancer affects the lower lip much more frequently than the upper lip and occurs almost 20 times more often in men than in women. It is seen more in the white than in the negro races, mainly after the age of 55, and more in those with outdoor occupations than indoor, possibly in relation to exposure to wind and sunlight.

The authors, who have made a study of tumours of the mouth at the University of Tennessee College of Medicine, Memphis, do not think that tobacco smoking or syphilis is concerned in causation, but that bad teeth and gums might be a factor, as the condition was uncommon in edentulous patients or those whose teeth and gums were in good condition.

The 5-year survival rate for the patients with cancer of the lip whose course could be followed was 69%. Most malignant tumours of the tongue occurred on the lateral border and were epidermoid carcinomata, which in the early stages closely resembled chronic ulcers due to trauma from dentures. The 5-year survival rate in these cases was only

27%. Cancer of the buccal mucosa was found nearly always to be associated with poor oral hygiene, decayed teeth, and jagged crowns or retained root tips. Among patients with carcinoma of the palate males predominated over females in a proportion of 7 to 1, and 90% of them were tobacco users. Most of the growths were ulcerated and not fungating and almost all were adenocarcinomata. Leucoplakia was found in all types of cancer of the oral cavity, with an average in all lesions of about 25%.

Thomas Hunt

989. **Cylindromata of the Upper Respiratory and Digestive Tract.** (I cilindromi delle vie aero-digestive superiori)
C. RIMONDI and A. D'ETTORRE. *Radiobiologia, radioterapia e fisica medica* [Radiobiol. Radioter. Fis. med.] 16, 427-439, 1962. 5 figs., 20 refs.

The cylindroma is a histological type of salivary gland tumour, of variable malignancy. After reviewing the literature, the authors report on a series of 18 cases treated at the University of Bologna, Italy, and give details of technique, radiation dosage, and results. They agree with the accepted view that the best method of treatment is primary radical surgery plus postoperative irradiation, and irradiation for recurrence or metastases. In some operable cases complete disappearance may be obtained by irradiation alone. In 4 cases subjected to previous repeated excisions, cure for up to 10 years followed irradiation. Various techniques were used, including interstitial radium, peroral short-distance x rays, and external x rays; dosage varied between 3,200 and 7,500 r. Distant metastases may occur after, for example, 6 years. A patient in whom pulmonary secondary growths were irradiated was alive 5 years later. In cases regarded, on histological grounds, as benign, there were no recurrences or metastases. At 5 years, 65% of the patients were alive, most of them clinically cured.

J. Walter

STOMACH AND DUODENUM

990. **Zollinger-Ellison Syndrome Treated with Poldine Methyl Methosulphate**
R. S. LAWRIE, A. W. R. WILLIAMSON, and J. N. HUNT. *Lancet* [Lancet] 1, 1002-1004, May 12, 1962. 8 refs.

A patient at Guy's Hospital, London, was considered to have the Zollinger-Ellison syndrome because he had 3 jejunal ulcers and a very high rate of gastric acid secretion; no abnormality, however, was observed in the pancreas at laparotomy performed for perforation of one of the jejunal ulcers. Treatment with large doses of poldine methyl methosulphate ("nacton") produced symptomatic relief, a fall in acid secretion to almost nil, a reduction in pepsin secretion to about one-quarter of the control amount, and a slowing of gastric emptying. Five months after the drug was discontinued the acid secretion was still virtually nil.

Although poldine is usually considered to act by blocking vagal excitation of the parietal cells, this is not considered an adequate explanation of its effect in the present case, as

vagal section is usually of no therapeutic value in such cases. The authors suggest that its anticholinergic effect may have been exerted on peripheral nervous plexuses, whose reactivity is essential for the full parietal response to histamine. It is possible that cholinergic excitation was the cause of the hyperplasia of gastrin-producing cells, and that this excitation was blocked by the drug. They consider that poldine, given in gradually increasing doses until side-effects are apparent, may be worth a three-week trial as an alternative to total gastrectomy in patients presumed to have the Zollinger-Ellison syndrome.

A. Gordon Beckett

991. **Gastritis; Present Position. An Analysis of 1,000 Consecutive Gastric Biopsies.** (Las gastritis. Estado actual del problema. Análisis de 1.000 biopsias gástricas consecutivas).

J. VALENCIA-PARPARCEN and H. ROMER. *G.E.N. Organó oficial de la Sociedad Venezolano de gastroenterología* [G.E.N. (Caracas)] 16, 309-332, Jan.-March [received June], 1962. 5 figs., bibliography.

The authors, writing from the Central University of Venezuela, Caracas, report the results of gastric biopsy in 1,000 patients. A Wood's tube was used and 948 satisfactory specimens were obtained; 271 (27.1%) were abnormal, 8 revealing gastric carcinoma and 263 various types of gastritis. Histological evaluation was based essentially on the criteria of Palmer. Superficial gastritis was present in 206 specimens, atrophic gastritis in 46, acute gastritis in 8, gastric atrophy in 2, and hypertrophic gastritis in one case. Most of the cases of acute gastritis were seen in the age group 10 to 29 years, and the condition was present more often in females than in males. Superficial gastritis occurred mainly in the 20 to 59 age group, and atrophic gastritis in the 30 to 69 age group, males predominating slightly in each case. The commonest symptom was abdominal pain. Histological features of gastritis were found in 88.3% of patients who had had gastrectomy, in 40.3% of those with gastric ulcers, in 17.0% with duodenal ulcers, in 41.7% with clinical gastritis, in 53.3% with gastric carcinoma, and in 33.3% with intestinal malabsorption. A histamine gastric function test was carried out in 677 patients, 343 of whom had no histological lesions. Achlorhydria was present in 23 of these, the remaining 320 having normal acidity. Achlorhydria or hypochlorhydria occurred in 40.0% of patients with acute gastritis, in 50.8% with superficial gastritis, and in 68.5% with atrophic gastritis.

M. Lubran.

992. **Gastric Secretion in Relation to Subsequent Duodenal Ulcer and Familial History**

J. H. BARON. *Gut* [Gut] 3, 158-161, June, 1962. 2 figs., 6 refs.

The only way to ascertain whether gastric hypersecretion produces peptic ulcer or is secondary to it is to follow up a group of subjects whose gastric secretion has been measured. In 1934 Lee Lander and MacLagan (*Lancet*, 1934, 2, 1210) measured the gastric secretion in response to 0.75 mg. of histamine in 100 healthy medical students. The present author, at the Middlesex Hospital, London, has followed up these 100 men: 3 had died and 5 could not be traced. Of the remaining 92, 91 answered a questionnaire requesting details of their medical and family histories. The answers showed that 7 doctors had developed a duodenal ulcer proved radiologically, 13 had suffered from dyspepsia for

which no definite diagnosis had been made, 2 had had dyspepsia attributed to hiatus hernia and oesophageal reflux, and 69 had never had any dyspepsia. There were no statistically significant differences between the 7 who had had duodenal ulcer and the 69 who had had no dyspepsia; but the mean secretion of free acid and volume of gastric juice were slightly higher in the ulcer patients. Of the dyspepsia-free subjects, 15 (22%) secreted less acid than the least amount secreted by any of the men who later developed duodenal ulcers. When the subjects were divided according to their family histories, the differences between the groups were even less marked.

Richard Doll

993. **Achieving "Physiological Gastrectomy" by Gastric Freezing: a Preliminary Report of an Experimental and Clinical Study**

O. H. WANGENSTEEN, E. T. PETER, D. M. NICOLOFF, A. I. WALDER, H. SOSIN, and E. F. BERNSTEIN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 439-444, May 12, 1962. 4 figs., 4 refs.

A method of controlling massive gastric haemorrhage by local gastric cooling has previously been described. The cooling was by continuous perfusion of a mixture of absolute alcohol and ice-water through an inlying gastric balloon to give a mucosal temperature of 10° C. to 14° C. In the present paper from the University of Minnesota Medical School, Minneapolis, the authors report observations at a lower range of temperatures, with particular study of gastric freezing as a treatment for chronic duodenal ulcer.

With absolute alcohol as the coolant, inflow temperatures as low as -17° to -20° C. were obtained. Gastric freezing at this inflow temperature for periods exceeding one hour was well tolerated, without any damage to the gastric mucosa, by dogs and by human beings. At this inflow temperature the mucosal temperature was maintained at -10° to -15° C. during at least half the period of perfusion. In dogs, after gastric freezing at this temperature for one hour the stomach usually became completely or almost completely achlorhydric, and significant depression of gastric secretion persisted, but without impairment of gastric emptying. Isolated gastric pouches when frozen for one hour became unresponsive to physiological stimuli, and in some cases this persisted for as long as 5 months afterwards.

Gastric freezing at various temperatures was carried out in 24 patients suffering from chronic duodenal ulcer with active symptoms. A balloon (of recently improved design) attached to the end of a double-lumen tube was passed into the stomach of the fasting patient, the throat being anaesthetized with 5% hexylcaine hydrochloride. A warming blanket was placed under the patient to prevent undue loss of body heat; rarely were declines of more than 1° to 2° C. observed. The inflow and outflow temperatures were carefully regulated and recorded at intervals of 5 minutes throughout the period of cooling. One or two hours after termination of gastric freezing the patient almost invariably ate with relish. Patients treated in this way for ulcer were allowed a general diet, the only dietary restriction being in respect of alcohol and caffeine.

Following the period, usually one hour, of gastric freezing all 24 patients had subjective relief of symptoms and showed a significant decrease in overnight secretion of free hydrochloric acid and in gastric secretory responses. In 10 patients, who underwent gastric freezing at an inflow tem-

perature of -17° to -20° C. for one hour, the decreases in free hydrochloric acid and in gastric secretory responses were very considerable. No impairment of gastric emptying time was observed. Symptomatic relief was "quite regularly" followed by radiological evidence of healing of the ulcer. [No further details of this evidence are given.]

The physiological and chemical changes produced by a single session of profound freezing of the gastric mucosa are described as amounting to a "physiological gastrectomy". Further observations for a much longer period will be necessary in order to ascertain how long the effects will continue. It is suggested that the procedure could be repeated in the out-patient clinic. The authors conclude that the procedure described is "a useful agent in the control of many of the manifestations of the peptic ulcer diathesis". [It would be interesting to have details of the duration of observations on these patients up to the date of this report.]

Joseph Parness

994. **Loss of Plasma Albumin Via the Intestine as a Cause of Hypoproteinaemia.** (Pérdida de albumina plasmática por el intestino como causa de hipoproteínemia) J. M. LINAZASORO, C. JIMÉNEZ DÍAZ, and M. CRIADO ORTIZ. *Revista clínica española* [Rev. clín. esp.] 85, 250-252, May 31, 1962. 7 refs.

Albumin turnover studies following the intravenous injection of 25 to 50 μ c. of radioactive albumin [presumably ^{131} I-labelled; this is not stated in the paper] were carried out in 7 patients with oedema, diarrhoea, and hypoproteinaemia, diagnosed as "protein-losing enteropathy". The mean total albumin pool was 2.47 g. per kg. (normal 4.32), plasma albumin pool 0.95 g. per kg. (normal 1.54), the half-time of plasma albumin 3.74 days (normal 7.03), half-life of total albumin 7.35 days (normal 18.9), and percentage catabolism 23.5 (normal 10.2). In 4 cases intestinal contents were aspirated during the half-hour after injection of radioactive albumin. The trichloroacetic acid precipitate contained 40 to 70% of the activity of the fluid. These results are in keeping with an intestinal loss of albumin. M. Lubran

LIVER AND GALL-BLADDER

995. **Haemochromatosis and Alcoholism.** (Hémochromatose et alcoolisme) M. CACHIN, F. PERGOLA, and P. VÉRON. *Semaine des hôpitaux de Paris* [Sem. Hôp. Paris] 38, 1773-1777, May 26, 1962. 22 refs.

At the Lariboisière Hospital, Paris, liver biopsy was performed on 428 alcoholic subjects; 240 were found to have cirrhosis, 84 to have pre-cirrhotic lesions, and the remainder to have fatty or normal livers. Siderosis of varying severity was found in about half of the cirrhotic and pre-cirrhotic livers and, to a much smaller degree, in the normal and relatively normal livers. Where the siderosis was heavy, tests were carried out to determine whether the case could be considered one of haemochromatosis. Gastric biopsy was performed in order to determine the presence of iron in the mucosa, and the degree of saturation of siderophilin (transferrin) in the plasma was measured. It was concluded that 22 of the patients with cirrhosis and one of those with pre-cirrhotic lesions were suffering from haemochromatosis. There are 2 ways in which haemochromatosis may arise in

alcoholism. The first is that the alcoholism may produce the disease, and the second is that alcoholism may reveal the disease where there is a genetic defect in iron metabolism. These mechanisms are discussed in detail and it is concluded that, while both occur, it is not at present possible to determine the relative frequency of acquired and of familial haemochromatosis. The authors consider that studies with radioactive iron may possibly throw light on the problem.

W. H. Horner Andrews

996. **Differential Diagnosis of Jaundice: Report of a Prospective Study of 61 Proved Cases**

S. SCHENKER, J. BALINT, and L. SCHIFF. *American Journal of Digestive Diseases* [Amer. J. dig. Dis.] 7, 449-463, May, 1962. 1 fig., 14 refs.

All patients with jaundice admitted to the Cincinnati (Ohio) General Hospital or Veterans Administration Hospital between October 1, 1958, and April 30, 1959, were examined by one or more of the authors and a provisional diagnosis was made on the history and clinical condition. Biochemical tests were then carried out and the diagnosis reviewed. Out of 95 cases seen, a definite diagnosis was made by means of hepatic biopsy or at necropsy in 67. Of these, 61-30 with cirrhosis, 20 with obstructive jaundice, and 11 with viral hepatitis—are considered in this report. Over 70% of the diagnoses made on clinical criteria alone were proved correct; when biochemical data were also considered, the number of correct diagnoses increased, but not markedly.

The clinical data are presented in tabular form. The average age of patients with cirrhosis (mostly males) was 47 years, with obstructive jaundice 68 years, and with viral hepatitis 37 years, but there was a considerable overlap in the ages. Abdominal pain was present in all three conditions, but was especially prevalent in obstructive jaundice, and if relief was obtained by a change of posture the cause was almost always pancreatic carcinoma. A history of alcoholism, especially when there was a recent increase in the consumption of alcohol, was commonest in cirrhosis, which was also the only condition to have a history of poor nutrition. An influenza-like onset or a history of contact with a case of hepatitis or of receiving blood transfusion usually denoted viral hepatitis. Various factors proved to be useless diagnostically; these included the duration and degree of icterus on admission, nausea, vomiting, loss of weight, pruritus, and a distaste for tobacco.

Physical signs of use in diagnosis were almost entirely confined to those present in cirrhosis—for example, spider angiomas, palmar erythema, or distended abdominal veins—but a palpable gall-bladder was noted only in obstructive jaundice (6 out of 20 cases). Of the laboratory data, the most useful appeared to be the following. In cirrhosis there was a lowered serum albumin level and a raised serum globulin level; the zinc sulphate turbidity was frequently raised above 21 units. In obstructive jaundice a positive cephalin flocculation reaction was rare, but the alkaline phosphatase level was almost always high; urinary urobilinogen excretion was low or absent. In viral hepatitis there was frequently a greatly raised transaminase level, this being significant in the early stages of the jaundice.

In confirming the diagnosis in cases of jaundice the authors suggest that percutaneous liver biopsy may prove of value, especially when there is a conflict between the clinical picture and the laboratory findings.

W. H. Horner Andrews

997. **Cholestatic Episodes In Jaundice due to Virus Hepatitis.** (Les épisodes cholestatiques au cours des icteres par hépatites virales).

G. ALBOT, A. M. JEZEQUEL, and J. LUNEL. *Acta hepatosplenologica* [*Acta hepatosplenol. (Stuttg.)*] 9, 140-154, May-June, 1962. 4 figs., 26 refs.

The authors, in this paper from the Hôtel-Dieu, Saint-Germain, Paris, recall that a transient recrudescence of jaundice, with a concomitant rise in plasma cholesterol and, sometimes, alkaline phosphatase levels, may occur in the course of viral hepatitis. This episode of jaundice is considered to be due to cholestasis, since no bile can be aspirated from the duodenum. In the 6 cases considered here (5 of which have been reported previously), the recrudescence occurred from 14 to 71 days after the first appearance of icterus. By optical microscopy of biopsy specimens it was seen that the changes in parenchymal cells tended to be focal, unlike the changes seen in typical viral hepatitis, in which the majority of cells show some degree of acidophil degeneration. Bile masses appeared, sometimes scattered throughout the lobule, but more commonly lying near the centre. In most of the livers there was less glycogen than is normally present, especially in the abnormal areas which were chiefly characterized by a clearing of the cells. The electron microscope showed that the majority of parenchymal cells were substantially normal, as judged by the appearance of the contained organelles. Degenerative cells were not common and regenerating cells were not seen. It may be concluded that diffuse parenchymal degeneration is virtually absent at the time of the cholestatic episode. There is an excess of bile pigment both in parenchymal and Kupffer cells, the picture differing from that seen in longstanding viral hepatitis in that here the bile masses were very large, resembling those present in mechanical biliary obstruction. Bile capillaries were irregular and did not connect directly with the space of Disse, but ruptures were seen in cell membranes through which bile capillaries, cytoplasm, and sinusoids were connected. Both bile canaliculi and the canals of Hering remained patent. Kupffer cells were huge and were filled with cell debris and bile pigment.

It is suggested that the cholestasis is due to overloading of parenchymal cells with pigment in viral hepatitis, leading to blocking of transport mechanisms. [It is not suggested, however, by what means recovery takes place from the episode, for the cells presumably become still further filled with pigment.]

W. H. Horner Andrews

998. **Electron-microscopic Observations on Human Liver during Cholestasis.** [In English]

F. ORLANDI. *Acta hepatosplenologica* [*Acta hepatosplenol. (Stuttg.)*] 9, 155-164, May-June, 1962. 9 figs., 13 refs.

The author, at the University of Perugia, has examined under the electron microscope biopsy specimens taken from the livers of 7 subjects, of whom 2 had iatrogenic jaundice and 5 had mechanical obstruction of the biliary tract. There was accumulation of a strongly electron-opaque substance in both the lysosomes and the cytoplasm of the parenchymal cells. In the lysosomes this substance was usually arranged in irregular concentric layers, though sometimes compact masses were seen. Its appearance in the cytoplasm, where it might be present unrelated to lysosomes, was similar, and again it tended to fuse into large masses which, on optical microscopy, appeared to be masses of bile. Occasionally the

masses were large enough to deform the cell outline, and sometimes communications between the masses and the space of Disse could be seen. Judged from the morphology of the surrounding organules, the bile masses were relatively well tolerated by the liver cells, but cytolysis of isolated cells did occur. The space of Disse was often dilated and the microvilli were more developed than usual. The canaliculi showed no constant changes, but were frequently dilated and contained bile masses. A considerable change was seen in Kupffer cells, which appeared to be hypertrophied and loaded with bile, which was present especially in lysosomes. The cells often occupied a large part of the sinusoidal space, and it appeared that the bile-containing lysosomes were discharging into the sinusoid and not into the space of Disse.

The hypothesis is put forward that the polarity of both the parenchymal and Kupffer cells is reversed, and that the lysosomes are not taking bile pigment towards the canaliculi but are actively discharging it, via the space of Disse, into the sinusoids. The author concludes that this is the mechanism of regurgitation in obstructive jaundice, and he was unable to show shunts between bile canaliculi and sinusoids.

W. H. Horner Andrews

999. **Non-icteric Forms of Infective Hepatitis and Their Epidemiological Significance.** (Безжелтушные формы эпидемического гепатита и их эпидемиологическое значение)

E. A. PAKTORIS and I. V. SHAGIL'DJAN. *Советская Медицина* [*Sovetsk. Med.*] 25, 71-78, May, 1962. 4 figs., 13 refs.

The percentage of cases of infective hepatitis in which jaundice is absent varies with different authors from 2.8 to over 33, depending largely on the criteria adopted. The present authors confine the term "non-icteric" to cases in which skin and conjunctival icterus is absent and the serum bilirubin level normal. They base the diagnosis on the clinical history, presence of hepatomegaly, and increased serum activity of glutamic-pyruvic and glutamic-oxalacetic transaminase (S.G.P.T. and S.G.O.T.) and of aldolase. While estimation of S.G.P.T. is more complicated than that of aldolase, it is more sensitive and the raised level persists longer. On this basis the authors investigated 28 sources of the disease (such as crèches, kindergartens, maternity and pre-school children's homes), and found 182 cases of infective hepatitis, of which 60 were non-icteric, 25 *formes frustes*, and only 97 icteric. In all, 2,530 estimations of aldolase and over 1,000 of S.G.P.T. and S.G.O.T. were made in 1,570 children. They were thus able to trace many cases which had escaped observation or had been incorrectly diagnosed, and to form a clearer picture of the spread of the epidemic, in which these non-icteric cases played a considerable part. Three important facts emerged from the investigations. (1) The proportion of non-icteric cases in all groups was much higher in the latter part of the survey, when laboratory methods were employed, than in the early stages when the diagnosis was made on clinical grounds alone. In this later stage the proportion of non-icteric to icteric cases rose to 3.5:1 in a total of 83 children. (2) The proportion of non-icteric cases was higher among children who had previously received prophylactic gamma-globulin (4.1:1) than in those who had not (2.2:1). (3) Non-icteric cases are as capable of spreading the disease as the others, and it is important that they be detected and isolated as soon as possible.

L. Firman-Edwards

1000. Portal Hypertension, Congestive Splenomegaly, and Portacaval Shunt

P. W. MORRIS, T. B. PATTON, J. A. BALINT, and B. I. HIRSCHOWITZ. *Gastroenterology* [Gastroenterology] 42, 555-559, May, 1962. 1 fig., 15 refs.

According to the authors the establishment of a portacaval shunt may correct the haematological abnormality in "hypersplenism"—consisting of anaemia, leucopenia, and thrombocytopenia—which occurs with portal hypertension. They review retrospectively 8 cases out of 34 in which a portacaval shunt had been constructed at the University Hospital and Veterans Administration Hospital, Birmingham, Alabama, between 1952 and 1960. There were 4 women and 4 men aged between 34 and 56 years.

In 6 of the 8 cases in which barium studies were made preoperatively, oesophageal varices were demonstrated, whereas after operation radiological studies in 5 patients showed no varices in 4 and diminution in size of varices in one. The spleen became smaller after operation in the 6 cases in which it was measured, and the haematological condition returned virtually to normal in all 8 cases. In 2 cases there was a relapse of the blood changes, thought to have been due to closure of the shunt, and this was confirmed at necropsy in one case. The relief was permanent in 4, but only temporary in 2 cases. In the remaining 2 cases follow-up was too short for definitive assessment of results.

It is concluded that portacaval anastomosis without splenectomy seems to be the most effective treatment of "hypersplenism" associated with portal hypertension, and may produce its beneficial effect by removing erythrocyte stasis in the spleen, which is regarded as a potent cause of the anaemia.

G. S. Crockett

INTESTINES

1001. Ileitis after Ileostomy: Prestomal Ileitis

W. R. THAYER and H. M. SPIRO. *Gastroenterology* [Gastroenterology] 42, 547-554, May, 1962. 2 figs., 30 refs.

This paper from Yale University, New Haven, Connecticut, discusses ileitis associated with ileostomy, and describes 4 cases. The clinical features were an increase in discharge (which was foul-smelling and copious enough to induce dehydration), abdominal cramps and distension; and, in some cases, bleeding. The ileum sometimes showed ulceration, sometimes polyposis. Obstruction at the stoma was inconstant. Some cases may represent regional ileitis, others the effects of obstruction, but the authors consider that the cause of ulcerative colitis may affect the ileum when the colon has been removed.

D. A. K. Black

1002. The Effect of Specific Foods and Water Loading on the Ileal Excreta of Ileostomized Human Subjects

P. KRAMER, M. M. KEARNEY, and F. J. INGELFINGER. *Gastroenterology* [Gastroenterology] 42, 535-546, May, 1962. 43 refs.

The object of this study from Boston University School of Medicine was to find out whether certain specific foods, which are either forbidden or recommended in the treatment of many intestinal disorders, do in fact have any effect on the intestinal excreta.

The study was made on 7 patients with well-established ileostomies, who were leading normal lives at home. The

stools were regularly collected and analysed, and the ileal effluent during 3-day control periods on a normal diet was compared with that during 3-day experimental periods on a diet which was identical except for isocaloric substitution of the food to be tested. The foods tested were milk, fried foods, pork, baked beans, cooked cabbage, fresh corn, dark rye bread, carbonated beverages, black pepper, prune juice, orange juice, and water. The average daily wet weight of ileal effluent was found to be 507 g. It contained, on average, 92.1% of water, 60.3 mEq. of sodium, and 3.6 mEq. of potassium per day. The bile pigment in the ileal effluent was mainly bilirubin, and this suggests that much of the stercobilinogen in stools is formed in the colon. The only substances studied which significantly altered ileal output were prune juice and cooked cabbage; they increased both wet and dry weight, the increase effected by prune juice being the greater and the more consistent. Baked beans increased the dry weight only. Milk (in moderate amount), fried foods, pork, corn, rye bread, carbonated beverages, black pepper, orange juice, and water did not alter the ileal excreta. Water loads of up to 3.5 litres per day in excess of normal intake were excreted in the urine and did not increase the volume of ileal discharge. The study thus suggests that "normal amounts of fried foods, pork, and orange juice can be eaten without fear that they will increase the amount of ileal content discharged into the colon".

Comparison of the characteristics of ileal effluent with those of normal faeces was used to assess colonic function. It indicated that the colon absorbs an average of about 60 mEq. of sodium and 400 ml. of water per day.

J. A. Farfor

1003. Primary Tumors of the Jejunum and Ileum: a Report of Nineteen Cases

R. B. QUATTLEBAUM JR. *American Journal of Surgery* [Amer. J. Surg.] 103, 558-563, May, 1962. 15 refs.

1004. Food Hypersensitivity in Ulcerative Colitis. Further Experience with an Intramucosal Test

J. A. RIDER and H. C. MOELLER. *American Journal of Gastroenterology* [Amer. J. Gastroent.] 37, 497-507, May, 1962. 4 figs., 12 refs.

Food hypersensitivity in patients with ulcerative colitis was studied, an intramucosal testing technique being used. A group of 20 patients with ulcerative colitis in partial remission were given injections of dilutions of milk, wheat, and eggs into the rectal mucosa; control patients without known organic disease received injections of saline or glycerin. Macroscopically a positive reaction consisted in immediate erythema followed within 5 minutes by a weal 1 to 2 cm. in diameter which persisted for about 30 minutes. Histologically there were acute vasculitis with swelling of the endothelial cells and perivascular infiltration with eosinophil and other cells.

In all the control patients the response was negative, but 16 of the 20 patients with ulcerative colitis gave positive reactions—13 to milk, 7 to egg, and 7 to wheat. Of 15 of these patients given diets lacking the foodstuffs to which they were sensitive, 10 went into complete or almost complete remission and 4 showed some improvement.

These findings suggest that allergic reactions to common foodstuffs may play a part in the aetiology of ulcerative colitis.

G. L. Asherson

Cardiovascular System

1005. Determination of the Hepatic Arterial Blood Flow and Oxygen Supply in Man by Clamping the Hepatic Artery during Surgery

N. TYGSTRUP, K. WINKLER, K. MELLEMGAAARD, and M. ANDREASSEN. *Journal of Clinical Investigation* [*J. clin. Invest.*] 41, 447-454, March [received May], 1962. 33 refs.

In 8 patients the hepatic artery proper was clamped for an average of 24 minutes during laparotomy. Hepatic arterial blood flow was calculated from hepatic venous blood flow (sulfobromophthalein method) and determination of hepatic and mesenteric oxygen consumption. This calculation implies a number of assumptions which are discussed in the text. The values of hepatic arterial blood flow given are presumably minimal, but apart from this the large scatter of the results may in part be due to methodological errors.

It was found that on an average: (1) the hepatic arterial blood flow was 35% (9 to 65%) of the hepatic venous blood flow; (2) the hepatic artery supplied 50% of the hepatic oxygen consumption; (3) the hepatic oxygen consumption was unchanged during the clamping; (4) the extraction percentage of sulfobromophthalein increased, and there was no significant release of transaminase during the clamping (the liver function was therefore assumed to be unaffected); (5) in 2 patients the portal pressure increased slightly; otherwise the portal and hepatic venous pressure remained constant during the clamping, and transhepatic and mesenteric resistance showed no significant change.

It is concluded that interruption of the hepatic arterial blood flow is initially compensated only by an increase of the portal-hepatic venous oxygen difference, and this seems to be sufficient to maintain normal liver function.—[Authors' summary.]

1006. The Left Bronchial Compression Syndrome. Left Atrial Enlargement and Dilatation of the Descending Aorta

J. M. RIVERO-CARVALLO. *American Journal of Cardiology* [*Amer. J. Cardiol.*] 9, 521-527, April, 1962. 9 figs., 13 refs.

A selected series of cases of left bronchial compression syndrome were studied at the National Institute of Cardiology, Mexico City, in an attempt to determine whether any standard patterns of symptoms and signs would facilitate diagnosis. Bronchial compression was due to left atrial enlargement in 600 patients and to aortic dilatation in 17. Most of the patients in the former group were aged 15 to 30 years; the patients in the latter group were between 40 and 50 years old. Compression was seen radiologically in all cases. In addition, tomograms were examined in 20 cases, angiocardigrams in 30, phonopneumograms in 100, and bronchograms in 5. At necropsy in 200 cases a considerably enlarged left atrium compressed the left main bronchus. In 90 of these cases the bronchus recovered its normal diameter immediately after dissection.

Clinically diagnostic signs included decreased movement of the left side of the chest, decreased vocal fremitus, diminished resonance, and a harsh loud inspiratory breath sound. Expiration was prolonged and harsh. It is pointed out by

the author that severe stenosis causes intermittent inspiration and that sudden left atrial dilatation results in paroxysmal dyspnoea associated with atelectasis of the left lung. The severity of the above signs parallels the degree of left atrial enlargement. The enlarged left atrium or aorta is best seen on a left anterior oblique radiograph and the left main bronchus on a penetrated postero-anterior view. Elevation of this bronchus was seen in 80% of the cases in the present series and backward displacement in 20%. The tracheobronchial angle was increased in 66% of the patients in whom it was measured.

The bronchial measurements in 100 of the patients were compared with those in 100 healthy subjects and showed an increase in length in 60 of the patients and a backward displacement in 20.

D. Goldman

1007. Pulmonary Veins in Left Ventricular Failure and Mitral Stenosis

J. P. LAVENDER, J. DOPPMAN, H. SHAWDON, and R. E. STEINER. *British Journal of Radiology* [*Brit. J. Radiol.*] 35, 293-302, May, 1962. 7 figs., 16 refs.

It has been established that in cases of mitral stenosis with raised left atrial pressure there is increased blood flow through the upper-lobe pulmonary vessels compared with the blood flow in the lower-lobe vessels. The authors of this paper from the Hammersmith Hospital and Postgraduate Medical School, London, describe investigations to determine whether a similar process occurs in left ventricular failure.

On tomograms of the right lung, the diameters of the upper- and lower-lobe veins were measured at specific sites, the ratio of the sum of the upper-lobe vein diameters to the sum of the lower-lobe vein diameters being termed the venous index. In a control group of 50 healthy subjects the venous index varied between 0.6 and 1; any index greater than 1 was, therefore, considered abnormal and indicative of relative increase in upper-lobe vein size. Of 36 patients with mitral valvular disease 29 had a venous index greater than one. In a group of 42 patients with left ventricular failure there were 18 with an abnormal index.

The possible causes of the abnormal venous pattern in left ventricular failure were studied. It appeared to be related to the duration rather than the severity of symptoms, because in 17 out of 36 patients with a history longer than 6 weeks there was an abnormal index, whereas of 6 patients with a history of less than 6 weeks only one had an abnormal index; further, approximately the same proportion with acute failure showed an abnormal index as in the group as a whole. It was also found that in those patients with a long history the incidence of peripheral [systemic] oedema was high and the incidence of paroxysmal nocturnal dyspnoea low in those with lower-lobe vascular constriction. This suggests that diminished lower-lobe blood flow in left ventricular failure is sometimes associated with raised left atrial pressure, pulmonary hypertension, and right ventricular failure, and that, as in mitral disease, this protects against pulmonary oedema.

Michael C. Winter

1008. The Natural History of 271 Patients with Mitral Stenosis under Medical Treatment

K. H. OLESEN. *British Heart Journal* [Brit. Heart J.] 24, 349-357, May, 1962. 3 figs., 7 refs.

This paper from Rigshospitalet, Copenhagen, describes a study of 271 cases of mitral stenosis first seen in the years 1933-49 and reviewed in 1951-3 and again in 1959. Patients with aortic valvular disease were excluded. Many patients had advanced disease when first seen; thus 57% had atrial fibrillation and 62% cardiac enlargement, and the presence of either of these factors worsened the prognosis. The mean age of the group when first seen was 41.5 years with a range of 14 to 73 years; women predominated over men in the proportion of 2.5:1.

By the time of the first follow-up, after an average period of 11 years, 70% had died, and after an average of 18 years 83% were dead, the mean age at death being 48. The causes of death were: congestive cardiac failure in 62%; thromboembolic phenomena in 22%; infection in 8%; and other causes in 8%. For the whole series the median survival time was 6 to 7 years. The women had a slightly higher survival than the men, and younger patients did better than those over 50. The prognosis in pure mitral stenosis was a little better than that in combined stenosis and regurgitation.

The author [rightly] stresses the seriousness and relentlessness of this disease.

G. S. Crockett

DIAGNOSTIC METHODS

1009. The Electrocardiographic Recognition of Left Ventricular Hypertrophy

I. ROSENFELD, C. GOODRICH, G. KASSEBAUM, A. L. WINSTON, and G. READER. *American Heart Journal* [Amer. Heart J.] 63, 731-742, June, 1962. 15 refs.

The authors of this study from the New York Hospital-Cornell Medical Center set out to examine the incidence and significance of changes in the electrocardiogram (ECG) in hypertrophy of the left ventricle (confirmed at necropsy), to determine the frequency of these changes in tracings from apparently normal hearts, to assess the effect of digitalis and myocardial infarction on such ECG changes, and to evaluate the reliability of routine radiography in the diagnosis of left ventricular hypertrophy (L.V.H.).

At necropsy the hearts of 135 patients with L.V.H., for whom complete clinical, laboratory, and pathological data were available, were examined and compared with 71 non-hypertrophied hearts. From their findings the authors conclude that the only reasonably sensitive and specific ECG criterion for the detection of L.V.H. appears to be increased voltage in Leads I and III; AVL, VI, and V5 (or V6). Prolongation of the ventricular activation time in the left precordial leads is specific but insensitive. The RS-T segment depression and T-wave abnormalities are sensitive but the least specific indications, being greatly influenced by digitalis and coronary disease. In the authors' view the routine chest radiograph is less reliable than is the ECG in the diagnosis of L.V.H., about half of the cases probably being missed. A normal ECG and straight cardiac radiograph by no means rule out the presence of L.V.H., nor does the abnormally high voltage of QRS always indicate such enlargement.

T. Sample

1010. Clinical and Kinetocardiographic Studies of Paradoxical Precordial Motion

J. C. DAVIE, J. O. LANGLEY, W. H. DODSON, and E. E. EDDLEMAN JR. *American Heart Journal* [Amer. Heart J.] 63, 775-807, June, 1962. 23 figs., 25 refs.

The kinetocardiogram is a graphic record of the precordial movements. Tracings are taken from positions over the praecordium which correspond to the V Leads in the electrocardiogram (ECG) and are designated K1, K2, K3, and so on. Other sites, such as the epigastrium, and the maximum thrust site when it is situated outside the usual areas, are also used. Simultaneous records of ECG Lead II and the carotid pulse are taken with the kinetocardiograms.

During systole the precordial area of the chest wall retracts in normal subjects except for brief, non-sustained outward movements during the very early part of ejection. In contrast, left or right ventricular hypertrophy and myocardial infarction often result in sustained systolic outward movement (paradoxical pulsation).

The authors of this paper from the Veterans Administration Hospital and the Medical College of Alabama, Birmingham, define these movements and point out the difference in the records of patients with certain types of heart disease. In those with hypertension and with acquired aortic valvular disease, the kinetocardiogram is more frequently abnormal than the cardiac radiograph or the ECG. Certain features of the tracing distinguish left ventricular thrust from right ventricular movement. Of patients with myocardial infarction 68% were found to have bulges in one or more precordial areas, often in the K2 or K3 position, and therefore unrelated to the usual site of maximum left ventricular thrust. The presence of a bulge in records from patients with conduction defects is evidence of underlying myocardial disease.

T. Sample

1011. Advances in the Auscultation of Cardiac Disorders. (Fortschritte in der Auskultation von Herzfehlern)

G. KAUFMANN. *Schweizerische medizinische Wochenschrift* [Schweiz. med. Wschr.] 92, 579-585, May 12, 1962. 5 refs.

The author, writing from the University of Zurich, discusses the contribution of phonocardiography in the diagnosis of heart disease. He describes in detail the auscultatory findings recorded on phonocardiograms of patients suffering from (1) aortic disease, including aortic incompetence, aortic sclerosis in the elderly, aortic stenosis, sub-aortic stenosis, and coarctation of the aorta; (2) pure mitral stenosis and mitral incompetence; and (3) abnormal communications between the systemic and pulmonary circulations, such as occur in atrial and ventricular septal defect, patent ductus arteriosus, and Eisenmenger's complex. Auscultation as a clinical diagnostic method has benefited from modern confirmatory procedures such as cardiac catheterization, angiocardiography, and heart surgery. Phonocardiography, in addition to providing an objective record of aural impressions, also establishes a precise time relationship between individual phenomena perceived by the ear, and between these and phenomena registered on the electrocardiogram and/or the phlebogram. It must be remembered (1) that phonocardiography gives maximum information only if recordings are obtained from at least 4 sites, namely, just external to the sternum in the right and left second intercostal spaces, in the left fourth or fifth intercostal space, and at the cardiac apex; and (2) that the human

ear is often superior to an instrument that records heart sounds, especially in picking up either very high frequency sounds, as in aortic incompetence, or sounds of low frequency, such as the diastolic sound that follows the third heart sound in mitral stenosis. The absence of a sound from a phonocardiogram can never be accepted as proof that it has not occurred.

E. S. Wyder

1012. Retrograde Arterial Catheterization of the Left Heart by the Dotter-Seldinger Technique. (Il cateterismo del cuore sinistro per via arteriosa retrograda mediante la tecnica di Dotter-Seldinger)

S. DALLA VOLTA, L. BUGARO, G. BATTAGLIA, and M. VINCENZI. *Malattie cardiovascolari* [Mal. cardiovasc.] 3, 111-126, March [received May], 1962. 9 figs., 31 refs.

This paper from the University of Padua reports experience with the Dotter-Seldinger method of retrograde arterial left heart catheterization. A plastic polyethylene catheter, one meter long and 2 mm. in external calibre, furnished with a flexible metallic guide, is introduced into the femoral artery. The metallic guide is withdrawn once the catheter has passed the aortic valve. The authors found the technique successful in 95% of the 108 cases, most of them of congenital heart disease, in which they used it. The technique failed in patients with very tight aortic stenosis, in whom Brock's direct transventricular puncture method was used. No significant complications occurred, apart from haematomata in the inguinal region in 3 cases. The authors consider the method suitable in both congenital and acquired heart disease.

A. J. Karlish

1013. Giant "a" Wave in Right Ventricular Overload. (Onda "a" gigante nei sovraccarichi ventricolari destri)

L. BUGARO, S. DALLA VOLTA, and M. VINCENZI. *Folia cardiologica* [Folia cardiol. (Milano)] 21, 1-22, Feb. 28 [received May], 1962. 6 figs., 45 refs.

Giant *a* waves were found in the right atrial pressure tracings of 61 out of 1,200 patients on whom cardiac catheterization was performed at the Medical Department of the University of Padua. The 61 patients included (a) 31 with isolated pulmonary stenosis, (b) 2 with Fallot's tetralogy, (c) 5 with idiopathic pulmonary hypertension, (d) 3 with patent ductus arteriosus and pulmonary hypertension, (e) 6 with ventricular septal defect and pulmonary hypertension, and (f) 14 with mitral stenosis and pulmonary hypertension. Cases of primary right atrial surcharge were excluded from the study. Systolic surcharge of the right ventricle was found in all cases in which giant *a* waves were present. The right ventricular diastolic pressure and the mean right atrial pressure were normal in all of the 61 cases, and there was no evidence of right ventricular failure.

In 5 of the 6 categories studied, a giant right atrial *a* wave appeared in every case when right intraventricular pressure exceeded 62 mm. Hg. In Fallot's tetralogy, on the other hand, a giant *a* wave appeared in only 2 of 60 cases. Conditions with right ventricular systolic hypertension and normal ventricular diastolic pressure in which the *a* wave was always normal included atrial septal defect, in which the *a* wave is increased only after the appearance of right ventricular failure. Giant *a* waves in the presence of pulmonary hypertension but without heart failure seem to indicate obstruction, of either valvular or pulmonary vascular origin, to the emptying of the right ventricle.

A. J. Karlish

CONGENITAL HEART DISEASE

1014. A Study of the Pulmonary Circulation in Congenital Heart Disease with Left-to-Right Shunt. (Étude de la circulation pulmonaire dans les affections cardiaques congénitales à shunt gauche-droit)

H. CLEEMPOEL, E. VAN THIEL, M. ENGLERT, and H. DENOLIN. *Cardiologia* [Cardiologia (Basel)] 40, 259-268, 1962. 2 figs., 22 refs.

The object of this investigation, carried out at the University of Brussels, was to determine whether the increased pulmonary output in left-to-right shunts in congenital heart disease is due to increase in velocity of blood flow or to increase in capacity of the pulmonary circulation.

Using dye dilution curves and a Cambridge oximeter, the authors found the velocity of blood flow in the pulmonary circulation (from pulmonary artery to peripheral artery) to be higher in cases of atrial septal defect, ventricular septal defect, and patent ductus arteriosus than in healthy controls, the increase in velocity varying with the degree of the shunt. When radioactive iodine was injected intravenously in patients with the same defects and the time of passage of the isotope (from right ventricle to left ventricle) measured, a similar increase in circulation velocity as compared with that in controls was demonstrated, and again the increase varied with the degree of shunting. Finally, when carbon monoxide absorption from the lungs was measured by the technique of Krogh as modified by Forster and co-workers (*J. clin. Invest.*, 1955, 34, 1417) in 19 cases of atrial septal defect and in 28 controls, only a slightly higher diffusion capacity was demonstrated in the former. If capillary pathology can be excluded, this indicates that pulmonary capillary volume is not increased in the same proportion as pulmonary blood flow. The increased blood flow must therefore be due to increased velocity. The authors conclude that in the presence of left-to-right shunt there is acceleration of transit in the pulmonary circulation as a whole, including its capillary sector.

H. G. Farquhar

1015. Pseudo-aortic Stenosis due to Idiopathic Hypertrophy of the Myocardium. (Stenosi pseudo-aortica da ipertrofia idiopatica del miocardio)

R. BENVENUTO and M. SERRATTO. *Cuore e circolazione* [Cuore e Circol.] 46, 1-17, Feb. [received June], 1962. 4 figs., 16 refs.

Idiopathic myocardial hypertrophic subaortic stenosis (or, briefly, hypertrophic subaortic stenosis) has recently been recognized as a cause of obstruction to left ventricular ejection. The aortic valve is normal and the obstruction, which is intraventricular, is due to narrowing of the outflow tract of the left ventricle as a consequence of myocardial hypertrophy of unknown origin. The similarity of the clinical picture to that of valvular, subvalvular, or supravalvular aortic stenosis has led in the past to errors of diagnosis and unnecessary operations. After reviewing the literature, the authors discuss the clinical, haemodynamic, and pathological features of the condition and report 3 cases seen at the University of Alberta Hospital, Edmonton. All 3 patients complained of anginal pains and 2 of syncopal episodes; all had a systolic ejection murmur along the left border of the sternum. The diagnosis was made during open-heart operation for what had been thought to be aortic stenosis. In one case the diagnosis of hypertrophic sub-

aortic stenosis was confirmed at necropsy. Recognition of this disease is important in the correct selection for surgery of patients with symptoms and signs of obstructed left ventricular ejection. No operative technique specifically adapted to the condition has yet been evolved. A few cases have been treated by making longitudinal incisions in the endocardium and extending them into the underlying myocardium at the site of the stenosis, but little improvement has resulted. The authors recommend a conservative attitude until the condition is better known and has been further studied.

A. J. Karlish

MYOCARDIUM

1016. Primary Myocardial Disease

N. O. FOWLER, M. GUERON, and D. T. ROWLANDS JR. *Diseases of the Chest [Dis. Chest]* 41, 593-602, June, 1962. 9 figs., 20 refs.

This paper from the University of Cincinnati, Ohio, describes 23 patients who were admitted to hospital in heart failure due to primary myocardial disease. The diagnosis was confirmed at necropsy in the 20 patients who died, and in the remainder myocardial biopsies were obtained at thoracotomy. All patients found to have an acceptable cause of myocardial dysfunction were excluded [although in 8 of those included a diagnosis of alcoholic cardiomyopathy would seem to be acceptable]. On histological examination, focal areas of myocardial fibrosis were seen in the hearts of 15 patients. None of the patients showed large areas of scarring, extensive subendocardial fibrosis or fibroelastosis, or evidence of active myocarditis in the form of accumulations of inflammatory cells. The heart weight was invariably above normal. Mural thrombi were present in 12 patients, systemic emboli in 4, and pulmonary emboli in 5. The authors confirm that primary myocardial disease is not rare although it may be difficult to distinguish from other forms of heart disease during life. Thus, isolated diastolic blood pressure readings of 100 mm. Hg or higher recorded in 5 patients suggested the possibility of hypertensive heart disease. A clinical diagnosis of chronic rheumatic carditis was made in 8 patients and of coronary artery disease in 5. One patient with a loud systolic murmur, an electrocardiogram (ECG) showing left ventricular hypertrophy, and on cardiac catheterization a gradient of 85 mm. Hg across the aortic valve (left ventricle 190/15 mm. Hg, aorta 105/65 mm. Hg) was subjected to thoracotomy, but no evidence of obstruction in the aortic valve or outflow tract of the left ventricle was found. In another patient a clicking early diastolic sound was interpreted as the opening snap of mitral stenosis, a diagnosis which seemed to be confirmed by the finding of left atrial enlargement on fluoroscopy. The authors also stress the difficulty in excluding pericarditis in the presence of recent or gross cardiac dilatation, feeble pulsation of the heart on fluoroscopy, elevation of venous pressure in association with clear lung fields, pulsus paradoxus, and elevation of right ventricular diastolic pressure. In older patients especially, the changes in the ECG in primary myocardial disease may be ascribed to coronary artery disease. In one patient in this series QS complexes in Leads II and III suggested posterior cardiac infarction, of which no evidence was found at necropsy. In none of the patients was the ECG entirely normal. Atrial

fibrillation was present in 8 patients, one developed atrial flutter after exploratory thoracotomy, and 4 had P waves suggesting right atrial hypertrophy. Abnormal left axis deviation was present in 6 patients, abnormal right axis deviation in 3, left ventricular hypertrophy in 8, and left bundle-branch block in 4. In 5 patients the QRS complexes were abnormally low.

Eirian Williams

1017. Arteriosclerotic Massive Hypertrophy of the Heart

H. J. VAN PEENEN and B. GERSTL. *Journal of the American Geriatrics Society [J. Amer. Geriat. Soc.]* 10, 505-508, June, 1962. 15 refs.

Coronary artery disease is usually thought to cause, at the most, only moderate cardiac hypertrophy; massive hypertrophy, when present, is attributed to concomitant hypertension. However, 26 cases of massive cardiac hypertrophy due to uncomplicated arteriosclerotic heart disease were seen at necropsy on 989 males at the Veterans Administration Hospital, Oakland, California, in the period 1956-9. The weight of the heart in all cases was 600 g. or more.

All 26 patients had a history compatible with coronary artery disease and all had died after prolonged heart failure. In none of them was there evidence of anaemia, other forms of heart disease, or renal arteriosclerosis; and none had a diastolic blood pressure above 90 mm. Hg. It is suggested that such massive cardiac hypertrophy may be due simply to prolonged heart failure.

T. B. Begg

1018. Dangers of Exercise Therapy in Organically Damaged Hearts. (Gefahren der Bewegungstherapie bei organisch geschädigten Herzen)

H. REINDELL and K. KÖNIG. *Medizinische Klinik [Med. Klin.]* 57, 769-774, May 4, 1962. 32 refs.

The authors have studied the effects of exercise therapy in patients with heart disease at the University Medical Clinic, Freiburg im Breisgau, Germany. Exercise consisted of running, swimming, cycling on level ground, non-competitive games, walks, and easy hill climbs. Each patient was given instructions as to the type, daily duration, and intensity of exercise. Previously the authors have discussed the indications and contraindications of exercise therapy in cardiac conditions. They described their method of determining heart size radiologically and of estimating cardiac reserve in terms of maximal oxygen intake, the relation of heart size to cardiac reserve being termed "heart-volume-function quotient". They discovered that the quotient lies between 40 and 70 in persons of 20 to 60 years, and that it rises with increasing age. A low "heart-volume-function quotient" indicates that the cardiovascular system is functioning satisfactorily, and *vice versa*. In the present paper they discuss the concept of "work-inadequacy", which is manifested in cardiac cases by (1) a high "heart-volume-function quotient", (2) pathological heart contours, and/or (3) increase in relative heart volume. From investigations on 5 patients with myocardial damage, who were suffering from "work-inadequacy", they conclude that: (1) when "work-inadequacy" is severe, admission to hospital, absolute rest in bed, and digitalization for 4 weeks are essential; when it is slight, the patient may be digitalized while ambulant; (2) "work-inadequacy" may occur in patients with a healed myocardial infarction; (3) when the "heart-volume-function quotient" has been brought to near-normal values exercise therapy should be instituted in

order to mobilize the patient to within the limits of his everyday needs, and to improve the cardiac reserve; (4) if exercise therapy is excessive it defeats these purposes and increases myocardial damage. Of the 5 patients, 3 cooperated well; their cardiac function improved, cardiac volume decreased, and "heart-volume-function quotient" fell. Two disregarded instructions and indulged in excessive exercise, with disastrous results.

E. S. Wyder

DISTURBANCES OF RHYTHM AND CONDUCTION

1019. **Implantation of an Internal Stimulator for Auriculo-ventricular Block in a Child of 7.** (Implantation d'un stimulateur interne pour correction d'un bloc auriculo-ventriculaire chirurgical chez une enfant de 7 ans) M. MOUQUIN, J. VAYSSE, M. DURAND, D. LAURENT, and L. SPROVIERI. *Archives des maladies du cœur et des vaisseaux* [Arch. Mal. Cœur] 55, 241-256, March [received June], 1962. 9 figs.

The authors describe an operation for correction of common atrio-ventricular canal which, using cardiac bypass and mild hypothermia (32° C.), they performed at the Broussais Hospital, Paris, in a child aged 7 years. They describe in detail the technique used to repair the fenestrated mitral valve and the aplastic tricuspid valve, and to close the foramen primum by simple suture. During the insertion of the posterior sutures for the latter procedure, complete atrio-ventricular block occurred and intramyocardial electrodes were inserted so that an external pacemaker could be used if necessary. It did become necessary and, after episodes of cardiac failure and eventually failure of the external stimulator to stimulate the heart, it was decided to use an internal pacemaker. This, weighing 170 g. and measuring 6.5 by 6 by 1.75 cm., gave a single-phase stimulus at a rate of 80 per minute, which, according to the authors, is preferable to slower rates. The duration of stimulation was 2 msec. with a current of 15 mA. and a potential of 8 volts. The 6 mercury batteries used were expected to have a life of 5 years. The apparatus was incorporated in epoxy resin, a cassette of steel, a further coat of resin, and a final covering of "teflon". The electrodes were of pure platinum, and the authors stress the importance of not touching these in order to avoid any tissue reaction to them. They were soldered to stainless-steel leads insulated with 10 coats of "teflon" and a siliconed rubber sleeve. The whole was sterilized with quaternary ammonium compounds and washed carefully with sterile physiological saline. This apparatus was inserted into the eleventh intercostal space and its prolongation behind the left kidney, and the leads brought through the costolumbar hiatus and passed separately through the pericardium. One electrode was sutured along the left border of the heart, the other in front of the right ventricle. To avoid traction on the electrodes, the leads should be sutured close to them in the form of a loop. The apparatus has worked satisfactorily for 8 months.

The advantages of an internal pacemaker are discussed, in particular the freedom it confers on the patient, and the avoidance of syncopal attacks and of cardiac hypertrophy. The disadvantages are the risk of electrical failure, the necessity for 2 operations if the machine has to be changed (detachable leads might avoid one of these), failure of the elec-

trodes to carry the stimulus, either because of displacement or because of tissue reaction around them; and, finally, the danger of a tissue reaction to the machine itself. The authors refer to possible improvements in the size and reliability of the apparatus, and to the remote possibility of a machine which will pick up the stimulus from the atrium and transmit it to the ventricle, thus permitting more physiological control of the heart than is possible with a fixed rate of stimulation.

H. G. Farquhar

1020. The Treatment of Quinidine-induced Ventricular Fibrillation by Closed-chest Resuscitation and External Defibrillation

C. R. RAINIER-POPE, V. SCHRIER, W. BECK, and C. N. BARNARD. *American Heart Journal* [Amer. Heart J.] 63, 582-590, May, 1962. 3 figs., bibliography.

Two young women admitted to Groote Schuur Hospital, Cape Town, with advanced rheumatic heart disease and atrial fibrillation, and who had previously had surgical repair of mitral incompetence, were treated with 45 gr. (2.9 g.) of quinidine orally over a period of 8 hours in order to restore sinus rhythm. Within about 3 hours both developed signs of toxicity to the drug—periods of hypotension, ventricular ectopic beats, and paroxysmal ventricular flutter and ventricular fibrillation with Stokes-Adams attacks. These attacks were treated with external cardiac massage and, when necessary, external cardiac defibrillation and assisted respiration. Other therapeutic measures included intravenous infusion of molar lactate solution, intravenous injection of hydrocortisone, and intramuscular injection of 20% magnesium sulphate solution. One patient survived after at least 14 paroxysms and made a good clinical recovery; 6 months later she was leading a normal life, and no attempt was made to correct the atrial fibrillation. The other patient had at least 90 paroxysms, and eventually these were abolished by intravenous infusion of procainamide. However, she soon developed irreversible hypotension, possibly due to summation of the effects of quinidine, procainamide, and cardiac and cerebral anoxia from so many attacks of ventricular fibrillation, and she finally died of cardiac standstill.

K. G. Lowe

CORONARY DISEASE AND MYOCARDIAL INFARCTION

1021. Glucose-loading ECG Test in the Diagnosis of Coronary Atherosclerosis

CH'EN TSAI-CHIA, CHANG YING-SHAN, PAI MAN-YI, HSÜ YI-SHU, and HWANG WAN. *Chinese Medical Journal* [Chin. med. J.] 81, 277-286, May, 1962. 3 figs., 9 refs.

It has been known for many years (Wayne and Graybiel, *Clin. Sci.*, 1933, 1, 287) that the taking of food can aggravate angina pectoris and produce ischaemic changes in the electrocardiogram (ECG) of patients who have ischaemic heart disease. In a study at Fu Wai Hospital, Peking, changes in the ST segment and T waves were produced in 81 out of 124 patients with coronary arterial disease after the ingestion of 100 g. of glucose. The changes were usually seen within 30 minutes and persisted for at least 1½ hours, and the greatest change did not necessarily coincide with the peak of the blood sugar curve. In 111 healthy young people the changes were absent or insignificant, and in 92 patients

with hypertension only one test gave positive results and 5 were borderline. There were no mishaps during the tests and there do not appear to be any contraindications.

In addition a Master 2-step test was performed on 72 patients with coronary arterial disease; the results were the same as those obtained with the glucose-loading test in only 13 cases, so that the tests may be complementary. The more common change after glucose ingestion was in the T wave, and after the Master 2-step test in the ST segment.

Intravenous injection of glucose in 3 patients produced the same changes in the ECG, thus disposing of the theory that the changes are due to gastric effect and consequent coronary arterial spasm. Ten patients had less marked changes when 2 g. of potassium chloride was given with the glucose.

It is suggested that the changes in the ECG are due to potassium-ion shift into myocardial cells, which are depleted of glycogen if the heart is ischaemic.

T. B. Begg

1022. Serum Mucoproteins and Plasma Fibrinolytic Activity in Coronary-artery Disease

D. OGSTON. *British Medical Journal* [Brit. med. J.] 1, 1242-1244, May 5, 1962. 1 fig., 12 refs.

It has been reported in the literature that in patients with atherosclerosis the serum mucoprotein level is raised. Published data on the plasma fibrinolytic activity in coronary artery disease are, however, somewhat contradictory. At the University of Aberdeen an investigation was undertaken to determine the relationship, if any, between the serum mucoprotein level and plasma fibrinolytic activity. The serum mucoprotein level and the plasma fibrinolytic activity were estimated in two groups of male patients—22 with no [apparent] atherosclerosis and 33 who had had a myocardial infarction 3 to 52 months previously. Most of the patients in the second group were receiving phenindione, but the serum mucoprotein concentration did not appear to be influenced by this drug, and in a previous study the author had found that plasma fibrinolytic activity was not affected.

The serum mucoprotein level was significantly higher in the post-infarction group than in the controls. In 14 of the 33 patients the level was clearly above the normal range (over 130 mg. per 100 ml.). In this subgroup of 14 patients there was significantly less lysis of plasma clots after incubation for 4, 8, and 24 hours than in the other post-infarction patients, and their body weight was significantly greater but not their height.

The author considers that further studies are necessary to elucidate the significance of these findings and their possible relevance to the pathogenesis of coronary artery disease.

T. B. Begg

1023. Thrombo-endarterectomy and Its Application to Coronary Artery Disease

P. R. ALLISON. *British Medical Journal* [Brit. med. J.] 1, 1641-1646, June 16, 1962. 4 figs., 19 refs.

The problems of ischaemic heart disease and of the mechanical effects of atherosclerosis are reviewed in this paper from the Nuffield Department of Surgery, Oxford.

The author discusses thrombo-endarterectomy and the part played by local arterial obstruction in the production of peripheral emboli. Coronary angiography is an important part of the detailed investigation of coronary artery disease.

The early demonstration of stenosis or complete obstruction

may well prove to be of vital importance in the assessment of the prognosis and in the selection of patients for surgical treatment. The most logical form of this, in the cases in which it is possible, is removal of the arterial obstruction. This work may in the future play an important part in the surgery of ischaemic heart disease, but, the author states, "if the history of anticoagulant therapy forms any sort of a parallel it will be a very long time before there is conclusive statistical support for surgical treatment".

Leon Gillis

1024. The Effect of Glucose-Insulin-Potassium Solution on the Electrocardiogram in Acute and Chronic Coronary Insufficiency. (Effets sur l'électrocardiogramme de la solution glucose-insuline-potassium au cours de l'insuffisance coronarienne aiguë et chronique)

D. SODI-PALLARES, A. DE MICHELI, G. MEDRANO, B. FISHLEDER, A. BISTENI, C. FRIEDLAND, and M. TESTELLI. *Malattie cardiovascolari* [Mal. cardiovasc.] 3, 41-79, March [received May], 1962. 23 figs., bibliography.

The potential difference across the membrane of the resting myocardial cell is related to the ratio between intracellular and extracellular potassium ions. Normally, this ratio is about 30:1 (150:5 mEq. per litre). With cellular death from cardiac infarction the ratio is greatly reduced. Surrounding the infarct is a zone of damaged cells with less reduced ratio, from which arises the cardiographic "current of injury". More distant from the necrotic centre of the infarct lie less damaged ischaemic cells which have a normal potassium content but a delay in the ionic interchange of repolarization at the end of systole; this produces depression or inversion of the T wave on the cardiogram.

This report from the National Institute of Cardiology of Mexico describes an attempt to improve the function of damaged but still viable cells after an infarction. Because it is known that muscle cells take up potassium when they absorb glucose, patients have been given potassium chloride, glucose, and insulin. The most effective preparation appears to be a litre of 5% glucose solution containing 40 mEq. of KCl and 20 units of soluble insulin, given intravenously. Shock should be overcome first, and the solution given slowly (40 to 60 drops per minute) so as to avoid overloading the circulation. Examples of cardiographic improvement are presented, chiefly correction of ST elevation after the infusion, and in one case permanent correction of T inversion. While improvement of electrical patterns may be achieved in this way, it still remains to be proved that this is more than would have followed by natural means, or that damaged cells are thus preserved from necrosis. However, this therapy merits further study, as it holds out some promise of relief of myocardial damage in the critical period following infarction before collateral circulation has begun to develop.

J. A. Cosh

1025. Effect of Different Dietary Fats on Blood Coagulation, Platelet Economy, and Blood Lipids

J. F. MUSTARD and E. A. MURPHY. *British Medical Journal* [Brit. med. J.] 1, 1651-1655, June 16, 1962. 2 figs., 28 refs.

The authors, at Sunnybrook Hospital, Toronto, have investigated the effects of certain variations in dietary fat on blood coagulation, platelet survival and turnover, and blood lipids. Seven male patients, 5 of whom had suffered from cerebrovascular or cardiovascular complications of atherosclerosis, were studied while receiving successively 3

rigidly controlled diets for a period of 4 or more weeks each. The diets were: (1) low in fat content; (2) rich in egg yolk and dairy fat; and (3) free from dairy products and with most of the fats from vegetable sources.

The coagulation studies included whole-blood clotting time, one-stage prothrombin time, the activity of plasma in place of serum in the thromboplastin generation test, platelet clumping time, platelet count, and platelet adhesive index. Platelet survival and turnover were studied by means of platelets labelled *in vivo* with diisopropyl fluorophosphonate containing radioactive phosphorus (^{32}P). [For details of the above techniques the original paper should be consulted.] Serum cholesterol was determined by the technique of Sperry and Webb, and serum phospholipid by the method of Zilversmit and Davis.

The coagulation studies showed the coagulant activity of the blood to be greatest during the period the subjects received Diet 2 (rich in egg yolk and dairy fat). The mean platelet-clumping time during this period was 223 seconds, whereas during the period on the low-fat diet (Diet 1) it was 335 seconds. Platelet survival was shortest and platelet turnover greatest when the patients received Diet 2. Platelet half-life was significantly longer when they were fed on Diet 1 than when they received Diets 2 and 3, and mean platelet turnover was least during the ingestion of Diet 1. Serum cholesterol and phospholipid values were highest during the period when Diet 2 was taken, but there was poor correlation between the level of blood lipids and the results of the coagulation tests.

In their discussion the authors review the literature on the relationship between diet, serum lipids, and atherosclerosis.

A. S. Douglas

1026. Cigarette Smoking and Coronary Heart Disease: Combined Experience of the Albany and Framingham Studies J. T. DOYLE, T. R. DAWBER, W. B. KANNEL, A. S. HESLIN, and H. A. KAHN. *New England Journal of Medicine* [New Engl. J. Med.] 266, 796-801, April 19, 1962. 27 refs.

In this paper from Albany Medical College, New York, a study is reported of the smoking habits of 4,120 men and the relationship of these habits to the subsequent development of coronary heart disease over periods varying from 6 to 8 years.

The men were between 30 and 62 years old at the outset of the study, and were considered to be free from coronary heart disease after detailed clinical and special examinations, including exercise electrocardiogram. Full details of past and present smoking habits were recorded. The examinations were repeated annually, but the smoking category of each patient remained the same as that on admission, in spite of changes in habit.

Cigarette smoking is associated with a death rate which, irrespective of cause, is significantly higher than that in non-smokers or in non-cigarette smokers. This increased mortality rate is largely due to coronary heart disease. The incidence of myocardial infarction, and of death from all causes, is 3 times greater in heavy cigarette smokers (more than 20 a day) than in non-smokers, pipe or cigar smokers, or former cigarette smokers. The death rate from coronary heart disease is 6 times greater in cigarette smokers than in the other categories. The incidence of angina pectoris is apparently unrelated to cigarette smoking. The mortality and morbidity rates of men who have ceased cigarette

smoking and of cigar and pipe smokers are similar to those of men who have never smoked tobacco at all.

J. Warwick Buckler

1027. α -Hydroxybutyric Dehydrogenase in the Diagnosis of Myocardial Infarction

L. PAGLIARO and A. NOTARBARTOLO. *Lancet* [Lancet] 1, 1043-1045, May 19, 1962. 2 figs., 12 refs.

In order to demonstrate that the enzyme hydroxybutyric dehydrogenase (S.H.B.D.) is present in the blood in increased amounts following myocardial infarction the authors investigated 30 cases of this disease at the Clinica Medica, University of Palermo, Italy. They noted the S.H.B.D. values one week, 2 weeks, and 3 weeks after the onset of pain. These were found to be raised in all cases during the first 2 weeks after infarction. In a control series normal values of S.H.B.D. were found in the absence of infarction, although raised values were noted in muscular dystrophy and to a lesser degree in cases of nephrosis and in cardiac failure.

The authors conclude that S.H.B.D. estimation is a useful test for the presence of recent myocardial infarction.

J. B. Wilson

1028. Transfusions of Blood and Blood Substitutes in the Treatment of Myocardial and Coronary Arterial Disease.

(О возможности переливания крови и некоторых кровезаменителей при различных поражениях миокарда и расстройствах коронарного кровообращения) Ю. В. КОФАНОВА. *Клиническая Медицина* [Klin. Med. (Mosk.)] 40, 41-47, May, 1962. 4 figs., 12 refs.

Transfusions of blood and of certain blood substitutes were given to 52 patients suffering from either myocardial or coronary disease. One of the blood substitutes was a 10% solution of sodium lactate; it was given alone or in combination with blood plasma. The transfusions were carried out by the drip method. There were no harmful effects. The beneficial effects consisted in slowing of the pulse, restoration of a normal electrocardiogram, and relief of pain. In some of the cases the transfusion was begun during a heart attack.

A. Orley

BLOOD VESSELS

1029. Cholesterol and Serum Turbidity Evaluation Measurements in Atherosclerosis

L. TOCHOWICZ, S. PASYK, and W. DENIKIEWICZ. *American Heart Journal* [Amer. Heart J.] 63, 760-767, June, 1962. 2 figs., 25 refs.

Hypercholesterolaemia and excessive postprandial lipaemia are accepted as common findings in coronary artery disease. The authors of this paper from the Cracow Academy of Medicine, Poland, found hypercholesterolaemia in 57% of 110 patients who had had myocardial infarction more than 6 months previously. (Hypercholesterolaemia is defined by the authors as a cholesterol level which is more than the average deviation above the reported mean level for a group of normal citizens of Cracow.) When 344 patients with myocardial infarction were given for 6 weeks or more a diet containing 2,000 Calories and only 12 to 15% of fat, hypercholesterolaemia was found in only 30%. It was present in 37% of 293 hypertensive patients.

Serum turbidity was measured before and 3 and 6 hours after a meal of 20 g. of animal fat, contained in 3 egg-yolks

and milk. In 120 patients with myocardial infarction and 300 with hypertension, excessive lipaemia in the fasting state or after the fatty meal was a much more constant finding than was hypercholesterolaemia, especially in males under 60 years of age. The authors suggest that a serum turbidity curve of this type is preferable to the serum cholesterol value as an index of disordered lipid metabolism of the type which predisposes to atherosclerosis.

T. B. Begg

1030. **Present State of Surgical Treatment of Obliterating Arteriosclerosis of the Abdominal Aorta and the Arteries of the Legs.** (État actuel du traitement chirurgical de l'artériosclérose oblitérante de l'aorte-abdominale et des artères des membres inférieurs)

J. HOFSTETTER and R. MOSIMANN. *Schweizerische medizinische Wochenschrift* [Schweiz. med. Wschr.] 92, 635-639, May 26, 1962. 5 figs.

The authors report their experience at the University Surgical Service, Lausanne, during the years 1960 and 1961, in the treatment of 150 patients with arteriosclerosis obliterans of the abdominal aorta or of the arteries of the legs. The mean age of the patients was 63 (range 23 to 94) years and 83% were males. All except 29 (19%) were treated surgically. The total mortality, mainly due to gangrene in the elderly, was 11%. Amputation, usually above the knee, was necessary in 40 cases (27%). Lumbar sympathectomy was done in 50 cases (33%), but [as usual] did not influence intermittent claudication, nor was it thought to modify trophic changes [possibly because these were too gross]. It is suggested that as the results obtained with drugs and with vessel grafts improve, there will be less place for sympathectomy. As a preliminary to vessel grafting, 65 transumbilical aortograms and 39 femoral arteriograms were made. Vessel grafts (44 in all) were inserted in 34 patients, and most were of the by-pass type. There was one postoperative death; 6 grafts thrombosed in hospital and 4 more within 5 months. There were 10 good results out of 15 cases followed up for 1 to 2 years and 6 of these 10 patients were active and had no symptoms. During the last 2 years the authors have carried out emergency surgical treatment in 11 cases of acute arterial obstruction. In 4 of the cases the aorta was obstructed, in 2 the iliac artery, in 4 the femoral artery, and in one the popliteal artery. The general state of the patients was often poor; there were 3 postoperative deaths, 4 poor results, and 4 successful results.

[Reconstructive surgical treatment of occlusive vascular disease of the abdominal aorta and lower limbs is undergoing re-appraisal in view of the relatively good prognosis for the limbs in the early stages of the disease. Unfortunately, few details of the clinical state of the patients are given and the reasons for inserting so many grafts are not stated.]

T. B. Begg

031. **Arteriosclerotic Aneurysms of the Circle of Willis. Some Notes on Their Morphology and Pathogenesis**

J. B. COURVILLE. *Bulletin of the Los Angeles Neurological Society* [Bull. Los Angeles neurol. Soc.] 27, 1-13, March (received May), 1962. 9 figs., 8 refs.

Aneurysms are sometimes found in the intracranial blood vessels forming the circle of Willis which do not seem to bear any direct relation to congenital malformations of these arteries, but rather to be part of a widespread arteriosclerosis.

The author describes their pathology, pathogenesis, and ultimate fate, and reports on the incidence of these lesions in necropsy statistics of Los Angeles County Hospital.

Aneurysmal dilatations of arteriosclerotic type which occur in later life can be classified on the basis of their shape: (1) saccular-shaped aneurysms almost invariably situated on the basilar artery, which can be subdivided into (a) miliary, (b) nodular, and (c) bulbous; (2) cylindrical swellings uniformly involving a segment; (3) fusiform dilatations occurring in the mid-portion of the basilar artery; (4) conical enlargements characteristically found in the terminal portions of the internal carotid arteries; (5) multi-segmental swellings; and (6) combined arteriosclerotic and congenital aneurysms.

Arteries which become the seat of such aneurysmal dilatations show varying degrees of arteriosclerosis, but are invariably elongated and tortuous, especially the basilar arteries. They may cause pressure on the right oculomotor and trigeminal nerves and on the left facial and auditory nerves. In most instances the lesions remain essentially quiescent throughout the individual's life, but their presence may be suspected by transitory or persistent double vision, pain suggestive of tic douloureux, or auditory symptoms; rarely sudden death from rupture may occur. In addition to pressure on adjacent structures, occlusion of the vessel from repeated deposition of blood clot may occur with subsequent softening of brain tissue.

A histological study of cross-sections from these enlarged vessels showed a diffuse hyaline change in the muscular coat of the vessel. This would imply a loss of the elasticity of the arterial wall which may render the vessel unable to maintain its original diameter against the usually coexistent but higher than normal blood pressure.

Among 40,000 necropsies performed over a 30-year period there were 3,315 (8.3%) instances of lesions of the brain due to arteriosclerosis with or without hypertension. In this group were 20 (0.6%) examples of unequivocal arteriosclerotic aneurysm, or one in every 166 cases of arteriosclerotic disease with changes in the brain.

A. Ackroyd

1032. **Mondor's Disease: a Superficial Phlebitis of the Breast** M. C. OLDFIELD. *Lancet* [Lancet] 1, 994-996, May 12, 1962. 2 figs., 18 refs.

This paper from the General Infirmary at Leeds gives 6 brief case histories of patients suffering from Mondor's disease, one of whom was a male. This disorder is defined as a superficial thrombophlebitis and periphlebitis of the subcutaneous veins radiating over the surface of the breast from the region of the areola towards the axilla, the epigastrium, or the subcostal margin. Although it is characteristically seen in women, there are many reports of its occurrence in men, and it may be seen at all stages of adult life.

Precipitating factors are repeated or unaccustomed exercise involving the pectoralis major muscle, particularly when the arm is raised above the head. The pressure of elastic clothing is probably an additional important factor. The clinical features are of a sudden onset of mild pain in the breast, and subsequently a "hard cord" is noticed at the site of the pain. The patient experiences no general malaise. On palpation a spindle or cord-like swelling radiating upwards and outwards or inwards and downwards is characteristic. Axillary lymph nodes are not enlarged. The skin is often adherent to the underlying cord and is tender and

red. The condition is self-limiting and the pain disappears within 10 days, but the cord remains for several further weeks. The attachment of the skin may remain for a year.

The author briefly discusses the differential diagnosis from carcinoma or an abscess, and emphasizes the value of this characteristic history and clinical findings. Treatment is conservative and consists only in support of the breast and arm. Local applications of heat may help to relieve the pain, but anticoagulants are unnecessary.

J. Warwick Buckler

1033. Prevention of Venous Thrombosis and Pulmonary Embolism in Injured Patients

G. ESKELAND. *Lancet [Lancet]* 1, 1035-1037, May 19, 1962. 6 refs.

The author reports a series of 150 patients, all over 55 years old, with fractures of the upper end of the femur treated at Ullevål Hospital, Oslo, Norway. Only those with clinical signs of venous thrombosis or definite conditions predisposing to thromboembolic disease were given anticoagulants. The results are contrasted with those in a somewhat similar series reported by Sevvitt and Gallagher (*Lancet*, 1959, 2, 981).

From a study of the combined results the author concludes that treatment with anticoagulants is required only in patients over 75 years of age, unless there is also a predisposition to thromboembolic disease or if any signs of venous thrombosis are present.

J. B. Wilson

LYMPHATIC CIRCULATION

1034. Regressive Mediastinal Adenopathy in Young Adults. (A Personal Series of 39 Cases.) (Les adénopathies médiastinales régressives de l'adulte jeune. (Étude d'une série personnelle de 39 observations))

C. LAGARDE, J. GUETTON, and G. LAURENS. *Journal de radiologie, d'électrologie et de médecine nucléaire [J. Radiol. Électrol.]* 43, 137-147, March-April, 1962. Bibliography.

The authors have studied 39 cases of mediastinal adenopathy found during 305,000 routine x-ray examinations performed at the Hôpital Maritime Sainte-Anne, Toulon, France, between 1947 and 1959. About 90% of the cases of adenopathy found were in males, but the majority of the subjects examined belonged to that sex. Of the 39 patients, 26 were aged between 20 and 30 years. Race or occupation did not play an important part in the incidence. In 34 of the patients there was no history of previous serious illness. In 5, symptoms of a variable type had led to the x-ray examination. There was no history of a similar condition in the parents or relations. In 5 of the cases, enlarged subcutaneous lymph nodes were present. In 23 cases fluoroscopy had been performed at intervals ranging from 3 months to 2 years previously, and had shown no abnormality. In no case was there radiological evidence of sarcoid involvement of the bones and on no occasion was *Mycobacterium tuberculosis* found in the sputum. The tuberculin reaction was negative or very faintly positive in 28 of the 37 cases in which the test was performed. In 5 subjects known to have a positive tuberculin reaction in the past, the reaction was negative at the time of examination. The blood count was normal in 21 cases; 14 cases had eosinophilia up to 10% (21% in a subject of coloured race). The

erythrocyte sedimentation rate was estimated in every case; it was normal in 29 and moderately raised in 10. Electrophoresis was carried out in 7 patients; the pattern was normal in 2 and in the others there was some increase in the beta-globulin fraction.

Bronchoscopy was performed in 16 cases; the findings were abnormal, but not characteristic, in 10. Specimens for biopsy were taken from the bronchi in 8 cases, but the findings were inconclusive. On x-ray examination of the chest, abnormal parenchymal pulmonary shadows were noted in 13 cases, usually in the form of a reticulation, but in some cases the shadows were nodular. Follow-up radiographs were obtained in 36 cases, and in 29 of these the lesions disappeared at intervals ranging from one month to 2 years. In 3 cases the lymph-node enlargement subsided after 2 years but the pulmonary changes remained. In only 2 cases did the nodular enlargement persist until the most recent control film made 3 and 4 years respectively after its discovery. Sarcoidosis was proved by biopsy in only 6 cases; in 4 of these the biopsy specimen was a peripheral node, in one a skin sarcoid which appeared several years after regression of the mediastinal adenopathy, and in one a pulmonary node examined during exploratory thoracotomy. The authors stress the similarity between these regressive lymph-node enlargements in young adults and sarcoidosis.

John H. L. Conway-Hughes

HYPERTENSION

1035. Arterial Pressure in an Industrial Population and Its Bearing on the Problem of Essential Hypertension

C. R. LOWE and T. McKEOWN. *Lancet [Lancet]* 1, 1086-1092, May 26, 1962. 11 figs., 14 refs.

In March, 1960, a mass radiography unit visited a large electrical engineering firm in Birmingham employing about 10,000 workers. Of these 7,234 (5,239 men and 1,995 women) attended for x-ray examination and their heights, weights, and arm circumferences were measured. In addition 12 doctors (4 at each session) recorded arterial pressure using mercury sphygmomanometers with standard cuffs. Readings were taken to the nearest 5 mm. or 10 mm. mark below the points at which sounds first appeared for systolic pressures and at which they first became muffled for diastolic pressures. The doctors recorded the age of the subject, parents (or their age at death) and, where relevant, the cause of death as (1) stroke, (2) heart disease, (3) cancer, (4) other and (5) unknown. The authors discuss the data relating to the males (5,239) subjected to x-ray examination.

Frequency diagrams of diastolic and systolic pressures are shown for the following age groups (numbers examined are given in brackets): 15 to 19 years (459), 20 to 29 (1,260), 30 to 39 (1,244), 40 to 49 (1,056), 50 to 59 (887), and 60 to 69 (333). The diagrams indicate that with increasing age mean pressures increase, and that distributions become flatter and asymmetrical with the longer tail on the side greater than the mean. [No results of formal tests of kurtosis or skewness are, however, quoted.] These diagrams offer no evidence of bimodality, nor do those showing the following distributions relating to men aged 40 to 59: (1) 602 men of whom one or both parents died at ages between 40 and 59, (2) 1,144 men whose parents lived after the age of 60, (3) 273 men with a parent who died from a stroke, (4) 42

men with a parent who died from heart disease, and (5) 370 men with a parent who died from cancer.

As previous reports of bimodal distributions in selected groups (for example, sibs of hypertensive probands) have been used as evidence in aetiological studies of essential hypertension, the authors discuss in some detail the absence of bimodal distributions in their data, with particular reference to factors which could result in apparent irregularities in truly unimodal distributions. They use data selected from their own series to demonstrate irregularities which could result from: (1) pooling pressures taken by different observers, (2) preference of observers for digits ending in zero even when reading to the nearest 5 mm. Hg, and (3) constructing frequency diagrams with too few measurements. They are convinced of the particular importance of this last cause of irregularities in distributions and show a relationship between the ratio of regular to irregular distributions and sample size for some 72 subgroups (and 12 combinations of subgroups) defined by observer and age group of subject.

The authors conclude as follows. "It is suggested that differences of opinion about the nature of essential hypertension arise chiefly from the fact that, defined as 'elevation of blood-pressure without apparent cause', it must include two different groups of cases: those in which no pathological condition is present and which can properly be regarded as the upper end of the distribution in the general population; and those in which associated pathological conditions are unrecognized. The proportion of the latter in a series from which recognized 'secondary' cases have been removed is probably much greater at very high than at moderately high levels of pressure."

E. A. Cheeseman

1036. Arterial Pressure and Hypertensive Disease in a West Indian Negro Population. Report of a Survey in St. Kitts, West Indies

R. E. SCHNECKLOTH, A. C. CORCORAN, K. L. STUART, and F. E. MOORE. *American Heart Journal* [Amer. Heart J.] 63, 607-628, May, 1962. 3 figs., 38 refs.

Blood-pressure estimations were made in 1,575 negroes, aged 20 to 49 years, who formed a representative sample of the rural population of the island of St. Kitts in the Leeward Islands. Mean pressures, both systolic and diastolic, were similar to those recorded in negro groups, but higher than those in white groups, of like age in the Bahamas and the United States. Higher mean pressures were recorded in Kittitian women than men over the age of 35 years. Both nulliparity and a history of toxæmia of pregnancy were associated with increased prevalence of hypertension. The only common manifestations of hypertensive vascular disease were mild retinal changes and slight proteinuria. There was no correlation between the dietary intake or urinary output of sodium chloride and the occurrence of hypertension. This study appears to support the view that the predisposition of American negroes to arterial hypertension is a racial trait.

K. G. Lowe

1037. A Cohort Study of the Blood Pressure of 444 Healthy White Males

R. M. THORNER. *Journal of Chronic Diseases* [J. chron. Dis.] 15, 117-130, Feb. [received May], 1962. 20 refs.

In this paper the author, writing from the United States Department of Health, Education and Welfare, Washington, D.C., has analysed the blood-pressure records of a selected

series of healthy white males whose blood pressure was repeatedly measured over a number of years. The subjects were all industrial executives, presumed to be free from disease, who attended a clinic for periodical routine medical examinations, usually at yearly intervals. The majority were aged between 40 and 60 years. For inclusion in the study a subject must have undergone 7 or more such examinations. Emphasis is laid on the fact that this is a highly selected group; in fact, 444 men fulfilled the criteria for selection out of a total of 1,363 who had attended the clinic 7 years before the date of analysis.

The results show that, although at the time of first examination there was a tendency for the mean blood pressure to be higher with increasing age, no definite upward trend was observed for the mean pressures of the group over the 7-year period, owing possibly to the relatively short time of observation. When the trends of individual blood pressures over the period were examined, it was found that of the systolic pressures 54% were upwards and 46% downwards, and of the diastolic pressures 48% were upwards and 52% downwards. These figures did not show any statistically significant trend in either direction. The actual blood-pressure measurements in individuals showed considerable variations from one examination to another.

A plea is made for further use of the longitudinal approach of studying the blood pressure in the same individual over a period of time, which might give a different picture from that obtained by cross-sectional studies of blood pressure in a number of different individuals of different ages at the same time.

M. Harington

1038. Hypertension Responding to Adrenolytics Though Not Due to Pheochromocytoma. (Ipertensione sensibili agli adrenolitici non causate da feocromocitoma)

P. PELLEGRINI. *Minerva cardiologica* [Minerva cardiologia] 10, 157-181, 10 figs., bibliography.

The author, writing from the University of Ferrara, draws attention to the use of adrenolytic drugs such as "regitine" (phentolamine hydrochloride) and piperoxane hydrochloride in the differential diagnosis of hypertension. It is not sufficiently widely known that in more than half the cases of pheochromocytoma hypertension is persistent rather than paroxysmal. That this condition is often missed is shown by two series of cases quoted, comprising together 250 patients, in 75% of whom the diagnosis was made at necropsy. Green in 1946 reported that of a surgical series of 51 patients 14 had paroxysmal and 37 had continuous hypertension. The present author's chief interest, however, is in hypertensive patients who react positively to phentolamine hydrochloride but have no pheochromocytoma. There is evidence that 5% of all hypertensive subjects may give this "false positive" result. About one in 3 of these have uraemia or chronic renal disease; the remainder may have hyperchromaemia, either functional or, in a small number of cases, due to lesions of the central nervous system. He quotes cases of his own and of other workers in which acute pulmonary oedema with hypertension did not respond to morphine or blood-letting, but responded dramatically to phentolamine hydrochloride administered intravenously; surgical exploration did not reveal pheochromocytoma in those cases. He suggests that all hypertensive subjects should be tested with this drug as a routine.

A. J. Karlish

1039. Methyldopa in the Treatment of Hypertension

R. I. S. BAYLISS and E. A. HARVEY-SMITH. *Lancet* [*Lancet*] 1, 763-768, April 14, 1962. 4 figs., 8 refs.

At Westminster Hospital, London, 20 patients with hypertension were treated with methyldopa in a dose of 250 mg. four times daily. All had severe hypertension as judged by the blood-pressure level (diastolic pressure over 120 mm. Hg in 17 of them) and its effect on cardiac, renal, and cerebral function, although only 7 had retinopathy of Grade III or IV. Of the 20 patients 19 showed a good initial response to treatment, with a fall in supine diastolic pressure to 100 mm. Hg or less. The patients were followed up for periods varying from 9 weeks to 12 months; in some cases an increase in the dose of methyldopa was necessary, while 4 patients became resistant to a daily dose of 3 or 4 g. after one or 2 months' treatment. Three patients with coronary artery disease were treated with benefit. The hypotensive action of methyldopa was potentiated by diuretic drugs of the benzothiadiazine group. Drowsiness occurred in the first few days of treatment in almost all cases, and sodium and water retention was a feature in 6 patients, but this responded to hydrochlorothiazide.

The particular advantages claimed for methyldopa are the regularity and smoothness of its action, its effect on lowering blood pressure, and the rarity of disturbing side-effects, especially postural hypotensive attacks. Its disadvantages are its failure to control very severe and malignant hypertension, the danger of left ventricular failure from fluid retention, and the large dose required. The authors consider that methyldopa may prove of most value in patients with Grade-III retinopathy, and in those with Grade-II retinal changes who are at risk from left ventricular failure or cerebrovascular accidents. *Bernard Isaacs*

1040. Cyclopenthiazide ("Navidrex") as a Hypotensive Agent

J. V. HODGE, F. O. SIMPSON, and G. F. SPEARS. *New Zealand Medical Journal* [*N.Z. med. J.*] 61, 258-265, May, 1962. 9 refs.

The object of this well-controlled trial at the Medical School, Dunedin, New Zealand, was to determine the optimum hypotensive dose of the new thiazide diuretic, cyclopenthiazide ("navidrex"). A series of 40 out-patients who were already receiving a thiazide diuretic with or without a ganglion-blocking or sympatholytic drug were given cyclopenthiazide in its place, but no other change was made in their treatment. The patients were divided into 4 groups of 10, each of whom received the drug in 2 different doses for 2 courses each of 2 weeks. Blood pressures were recorded in the standing and lying positions before and after each course. The doses used ranged from 0.5 to 4 mg. daily, and some patients were also given a placebo for a period.

The blood-pressure levels after the different courses were compared by an analysis of variance. A definite hypotensive effect, particularly in the standing position, was detected after a daily dose of 1 mg. of cyclopenthiazide, this effect being most marked in patients who were also receiving ganglion-blocking agents. The hypotensive effect of cyclopenthiazide increased with rising doses, the greatest effect being exerted by the 4-mg. dose. (In an addendum it is stated that an 8-mg. dose was no more effective and caused disturbing side-effects.) No side-effects were experienced with doses up to 4 mg., but a slight rise in serum levels of

uric acid and non-protein nitrogen and a slight fall in serum potassium level occurred during therapy.

It is concluded that cyclopenthiazide is a very satisfactory member of the thiazide group. The recommended dose for hypertension is 1 to 2 mg. daily. *Bernard Isaacs*

1041. The Treatment of Hypertension in General Practice with the New Preparation Repicin. (Die Behandlung der Hypertonie in der Praxis mit dem neuen Kombinationspräparat Repicin)

H. NEUN. *Wiener Zeitschrift für innere Medizin und ihre Grenzgebiete* [*Wien. Z. inn. Med.*] 43, 122-128, March [received June], 1962.

"Repicin", a new antihypertensive preparation, is a combination of a drug which lowers the blood pressure rapidly with one which keeps it low over a long period. Each tablet contains 2 mg. of 3-benzyl-6-trifluoromethyl-7-sulphaminy-3,4-dihydro-1,2,4-benzothiadiazine-1,1-dioxide, 0.1 mg. of reserpine, and 200 mg. of potassium chloride. The author has used it in 24 hypertensive patients who were not in hospital. He attributes the satisfactory result to reciprocal potentiation by the constituent hypotensive drugs rather than to an additive effect. The addition of potassium chloride to the formula obviates the danger of hypokalaemia. Only in one case did repicin have no effect. In 23 cases the average blood-pressure readings were 211/103 mm. Hg before and 168/90 mm. Hg after its administration, which was continued for 1 to 25 weeks (average 6 weeks). Indigestion occurred in 3 patients, but was readily relieved by administering the tablets with or after meals. The advantages of repicin are that only 1 to 2 tablets need be taken daily, and that a salt-free diet is not necessary, although the salt intake should be reduced. *E. S. Wyder*

1042. Guanethidine in the Treatment of Hypertension

K. N. V. PALMER and G. A. McDONALD. *Postgraduate Medical Journal* [*Postgrad. med. J.*] 38, 338-340, June, 1962. 6 refs.

The results obtained with the sympathetic blocking agent, guanethidine, in the treatment of hypertension are described in this paper from the University of Aberdeen. The drug was given for periods up to 20 months to 20 patients (16 female and 4 male), in all of whom the diastolic pressure before treatment was 120 mm. Hg or higher. Grade-IV retinopathy was present in 3 patients and Grade-III retinopathy in 4. The blood urea level was over 50 mg. per 100 ml. in 5 patients and 3 others had hypertensive heart failure. Essential hypertension was considered to be present in 18 of the patients, while in 2 the hypertension was thought to be secondary to chronic pyelonephritis.

All the patients were treated in hospital. Initially the dosage of guanethidine was 10 mg. daily; subsequently this was increased by not more than 10 mg. daily at 4-day intervals. If adequate control of blood pressure was not obtained with 60 mg. daily, a benzthiadiazine diuretic by mouth was added to the treatment regimen; this was necessary in 7 patients in the series. A satisfactory fall in the standing blood pressure was achieved in all the patients. In the majority retinopathy cleared up, proteinuria was reduced, and electrocardiographic evidence of left ventricular strain was abolished.

Side-effects were few and there was no evidence of drug tolerance. *M. Harlington*

Clinical Haematology

1043. Hyperfibrinolysis in Carcinoma of the Prostate.

(Hyperfibrinolyse bei Prostatakarzinom)

J. BREDT. *Blut [Blut]* 8, 22-28, March [received May], 1962. 2 figs., 32 refs.

At the City Hospital, Solingen, Germany, the author observed a case of metastasizing carcinoma of the prostate which had been admitted to hospital with the diagnosis of haemorrhagic state. The patient was a man of 62 who had skin haemorrhages, haematuria, bleeding gums, epistaxis, and severe anaemia. He had first noticed blood in the urine and stools about 4 weeks before admission. He had had no disturbance of micturition and the prostate was normal on digital examination. The cause of the haemorrhagic state was found to be fibrinolysis accompanied by a complex disorder of coagulation of the blood. Because of the fibrinolysis a biopsy specimen was taken from the prostate and its examination showed carcinomatous change. Bleeding continued and the haemoglobin level fell to 30%. Blood transfusion did not arrest the bleeding, but this ceased when the prostatic carcinoma was treated with "hönvan" (stilboestrol diphosphate). The patient lived another 3 years practically symptom-free and then died from pneumonia.

A. Brown

1044. The Use of Human AHF (Fraction I-O) in Haemophilia A. [In English]

M. M. NILSSON, M. BLOMBÄCK, B. BLOMBÄCK, and O. RAMGREN. *Blut [Blut]* 8, 92-101, April, 1962. 3 figs., 16 refs.

In this paper from the University of Lund and the Karolinska Institute, Stockholm, is described 5 years' experience in the use of human plasma fraction I-O, containing antihæmophilic factor, in the management of classic hæmophilia. In all, 63 cases of hæmophilia A received fraction I-O on 818 occasions. The successful treatment of bleeding episodes and the effective preparation of patients for major as well as minor surgery are described and discussed. In 3 cases prophylactic administration of fraction I-O at monthly intervals has been carried out for more than 2 years, during which time the frequency and severity of bleeding episodes appear to have been reduced.

A. Brown

1045. Population and Genetic Investigations on the Erythrocyte Factors Gy. (Populationsgenetische Untersuchungen über das Blutkörperchenmerkmal Gy)

F. SCHWARZFISCHER and K. LIEBRICH. *Blut [Blut]* 8, 161-166, May, 1962. 5 refs.

The authors, writing from the University of Munich, briefly describe their method of testing for the Gy factor in human erythrocytes. The method is based on the fact that Gy-positive cells suspended in 30% bovine albumin agglutinate on the addition of a ground-nut extract. The authors differ from Boyd and co-workers in finding that the reaction may not only be ++, +, and negative, but also ±. A survey of 709 blood donors was carried out in a total of 7 localities in two areas of Upper Bavaria and in one area of Swabia, the object being to detect regional differences and to determine any connexion between the A₁A₂BO-pheno-

types and the Gy type. The results are presented in tables and statistically evaluated. The incidence of Gy++ varied between 18% and 38%. The χ^2 test was applied and the differences between the regions were found to be statistically significant. Equivalent differences in the ABO and MN distribution in the same areas had been previously described. As Boyd *et al.* had found that certain ground-nut extracts reacted preferentially with Group-A cells, a study of the relationship between Gy and ABO systems was carried out. A statistically significant relationship between A₁A₂BO-phenotypes and the Gy type was found. Gy was found to be positive relatively more frequently than expected with groups A₁ and AB cells and less frequently with B, A₂, and O cells. On the other hand, it was seen that in the regional distribution of the material studied, Gy variation was independent of the ABO variation in the same areas.

F. Hillman

ANAEMIA

1046. Cyanocobalamin Therapy Effect in Folic Acid Deficiency

R. ZALUSKY, V. HERBERT, and W. B. CASTLE. *Archives of Internal Medicine [Arch. intern. Med.]* 109, 545-554, May, 1962. 5 figs., 41 refs.

In this paper from the City Hospital and Harvard Medical School, Boston, the authors describe 3 cases of megaloblastic anaemia due to folic acid deficiency which responded to large doses (500 µg. daily) of cyanocobalamin (vitamin B₁₂). In a trial period one of the patients had not responded to 1 µg. daily of the vitamin. It is suggested that the mechanism of the observed response was increased mobilization and/or utilization of folic acid caused by the "supraphysiologic" daily dose of cyanocobalamin. Urinary excretion of formiminoglutamic acid declined but remained abnormal while the patients were being treated, suggesting that the defect of the folic acid supply was not completely met. It is further suggested that for diagnostic purposes a therapeutic trial in patients with megaloblastic anaemia should be carried out with small daily doses of vitamin B₁₂, which will initiate a hæmatological response only in cases of cyanocobalamin deficiency. Large doses of the vitamin parenterally in patients with folic acid deficiency, like large doses of folic acid in cyanocobalamin deficiency, may produce a reticulocyte response and so lead to an incorrect diagnosis of either type of deficiency.

Janet Vaughan

1047. Erythroid Cell Maturation and Hemoglobin Synthesis in Megaloblastic Anemia

D. G. NATHAN and F. H. GARDNER. *Journal of Clinical Investigation [J. clin. Invest.]* 41, 1086-1093, May, 1962. 3 figs., 19 refs.

Recent observations of the rate of glycine uptake into heme and globin during normal erythrocyte maturation in man have led to the conclusion that heme and globin may be synthesized independently during the development of the mature erythrocyte. Globin appears to be maximally syn-

thesized at a primitive stage of erythrocyte development, whereas heme is maximally synthesized midway in maturation. The present authors, from the Peter Bent Brigham Hospital, Boston, now report studies on heme and globin synthesis in megaloblastic anaemias. Their data show: (1) that the maturation time of the primitive megaloblast is prolonged; (2) heme and globin synthesis appear to be synchronous during maturation of the megaloblastic cell; and (3) vitamin B₁₂ shortens the maturation time and may enhance globin synthesis in the primitive cell.

Janet Vaughan

1048. Pyridoxine-responsive Anemia

S. S. BOTTOMLEY. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 653-659, May 26, 1962. 7 figs., 44 refs.

This paper from the University of Oklahoma School of Medicine, Oklahoma City, reports 2 cases of hypochromic microcytic anaemia which responded to the administration of pyridoxine hydrochloride. The first patient was a 41-year-old male who also had haemochromatosis. Intramuscular injections of 200 mg. of pyridoxine produced a reticulocytosis followed by a rise of the haematocrit to a normal level. When the drug was discontinued the haemoglobin level and the haematocrit value fell. Another sub-optimal response was obtained when a further course of pyridoxine was given.

The second patient was a 40-year-old female whose symptoms of fatigability started during her 5th pregnancy. The anaemia was resistant to various haematinics, including vitamin B₁₂. The hypochromic microcytic anaemia was associated with hyperferraeemia. A reticulocytosis and a return of the haematocrit to a normal level followed treatment with pyridoxine. A tryptophan loading test indicated an abnormal urinary level of hydroxykynurenine, and this was corrected by pyridoxine administration. In this case also the hypochromasia and microcytosis persisted after the haemoglobin level had returned to or near normal.

It is suggested that a phosphorylating enzyme of pyridoxine may be implicated in this disease.

A. W. H. Foxell

1049. Iron Absorption from the Gastro-Intestinal Tract: a Reassessment of the "Mucosal Block" Theory and the Influence of the Rate of Erythropoiesis

S. CANTRILL and R. J. WALSH. *Australian Journal of Experimental Biology and Medical Science* [Aust. J. exp. Biol. med. Sci.] 40, 17-23, Feb. [received July], 1962. 1 fig., 18 refs.

The authors of this paper from the New South Wales Red Cross Blood Transfusion Service, Sydney, have re-examined the theory of a mucosal block preventing absorption of iron. Rats were given ferrous ammonium sulphate in drinking-water for 4 days and tracer doses of radioactive iron (⁵⁹Fe) were given at intervals after the loading iron was discontinued. It was shown that when the tracer dose of ⁵⁹Fe was given within 24 hours of the loading period there was a significant reduction in the amount absorbed, whereas after 24 hours the absorption rates, although very variable, did not approach the low figure obtained in the first 24 hours. In a second experiment erythropoiesis was stimulated by producing a haemolytic anaemia with phenylhydrazine. Over a period the haemolysis was compensated by increased erythropoiesis so that there was no reduction in the haemoglobin level. When this stage was reached

doses of ⁵⁹Fe were given and the amount absorbed was correlated with the reticulocyte count. In one group of rats with normal haemoglobin values given phenylhydrazine the reticulocyte count was 14% and the iron absorbed from the tracer dose was of the order of 28%; in a control group with an almost identical haemoglobin level but not given phenylhydrazine the reticulocyte count was only 1.5% and the proportion of tracer iron absorbed was 10%. These results indicate that although mucosal-cell block plays some part in the control of absorption of iron it is only effective for a few hours after the loading dose. On the other hand, the influence of erythropoiesis on iron absorption is much more marked. The rate of erythropoietic activity as measured by the reticulocyte count is correlated quite clearly with the amount of iron absorbed.

R. F. Jennison

1050. Iron Absorption from the Intestinal Tract: the Influence of the Iron Stores

S. CANTRILL, R. J. WALSH, I. BRADING, and E. P. GEORGE. *Australian Journal of Experimental Biology and Medical Science* [Aust. J. exp. Biol. med. Sci.] 40, 25-30, Feb. [received July], 1962. 15 refs.

In a second study of iron absorption from the intestinal tract (see Abstract 1049) two experiments were carried out on rats to determine the effect of the amount of iron in the storage organs on the absorption of iron from the gastro-intestinal tract. In the first experiment the total iron in the body was increased by injections of iron-dextran; 7 weeks after the end of the iron-loading period the amount of iron absorbed from a tracer dose of radioactive iron (⁵⁹Fe) was compared with the amount absorbed from a similar dose by control animals. In the second experiment rats were transfused with erythrocytes to increase the total body iron, and iron was also added to the drinking-water. The mean iron content of the blood, liver, and spleen of animals injected with iron-dextran was 82.3 mg., whereas in the controls the mean was 14.26 mg. The bulk of the extra iron was found in the liver; the haemoglobin iron was not increased. In the control rats 5.63% of the iron was absorbed, whereas in the animals given iron-dextran only 0.87% was absorbed. In the rats injected with erythrocytes the mean total iron content of the tissues was 15.33 mg. and in the controls it was 12.52 mg. The iron stores were less saturated by this technique, and this was reflected in the fact that although more iron was absorbed by the control animals (11.2%) than by the iron-loaded animals (6.1%) the difference was not nearly so marked as with the animals loaded with iron-dextran. There was recovery of only 34% of the iron in the iron-dextran experiments; approximately 27% of the iron injected in the erythrocytes was recovered.

The authors discuss the reasons for these low figures and suggest that whereas in human beings only negligible amounts of the total body iron are excreted, in animals an appreciable proportion of the iron in the body (approximately 0.5% a day) is lost. These experiments show that the amount of iron stores has an effect on the rate of iron absorption from the gastro-intestinal tract. It is known that in haemochromatosis the accumulation of iron in the organs does not prevent the absorption of further iron, and this implies that "the basic lesion in haemochromatosis must therefore include a lack of sensitivity of the factors regulating iron absorption to the size of the iron stores".

R. F. Jennison

1051. **Iron Absorption from the Intestinal Tract: the Influence of the Haemoglobin Concentration and of Hypoxia**
S. CANTRILL and R. J. WALSH. *Australian Journal of Experimental Biology and Medical Science* [Aust. J. exp. Biol. med. Sci.] 40, 31-36, Feb. [received July], 1962. 19 refs.

A controlling factor in the absorption of iron from the intestinal tract may be the haemoglobin level or reduced oxygen tension. Rats were rendered polycythaemic by transfusion. The mean haemoglobin level in the polycythaemic rats was 18.3 g. per 100 ml. and 0.57% of the dose of iron administered was absorbed, 45% of this being found in the liver, spleen, and kidneys. In normal rats the haemoglobin level was 15.6 g. per 100 ml. and 2.38% of the dose of iron was absorbed; only 14.4% of the absorbed iron appeared in the organs. Rats exposed to air and to air with 5% carbon dioxide absorbed roughly the same amount of iron, but those exposed to air with only 11% oxygen absorbed 50% more of the dose of iron.

It is suggested that the depressed absorption of iron in the rats with polycythaemia may be due to the iron from the injected erythrocytes accumulating in the stores and thus depressing absorption, or to the polycythaemia causing a depression of bone-marrow activity and consequently less call for iron. This is similar to the depression of erythropoiesis in human beings following blood transfusion. The results of the experiments with the different atmospheres suggest that reduced oxygen tension has a direct effect on the absorption of iron. This may be directly on the intestinal mucosal cells or some other organ producing an intermediary substance, such as xanthine oxidase or erythropoietin.

R. F. Jennison

1052. **Massive Generalized Haemochromatosis Associated with Hypochromic Hypersideraemic Anaemia Responding Incompletely to Pyridoxine.** (Hémochromatose massive et généralisée associée à une anémie hypochrome hypersidérémique incomplètement sensible à la pyridoxine)
J. CAROLI and J. ANDRÉ. *Semaine des hôpitaux de Paris* [Sem. Hôp. Paris] 38, 1621-1637, May 14, 1962. 10 figs., 51 refs.

The authors, from Saint-Antoine Hospital, Paris, describe in detail the clinical and laboratory findings during the last 4 years of the life of a patient suffering from hypochromic anaemia which was partially sensitive to pyridoxine. They divide the illness into 3 stages: (1) the stage in which the diagnosis was established; (2) the stage during which various treatments, in particular pyridoxine, were tried; and (3) the stage in which the patient died from haemochromatosis with diabetes and cachexia. Although no identical condition could be confirmed in members of the patient's family, features such as mild hypochromic anaemia in certain relatives and the histories of others who had died suggested a possible relationship.

Cases described in the literature are reviewed from both the aetiological and the therapeutic aspects. The disease is often hereditary, is probably related to sex, and generally appears later rather than earlier in life. It is always attended by hypersideraemia, with high saturation of the plasma siderophilin. It is usually refractory to all forms of medication except pyridoxine, to which the response is variable. Radioisotope studies show that the uptake of iron from the digestive tract is increased, as is the turnover

of iron in the erythrocyte population. This combination of exaggerated digestive uptake and excessive erythrocyte destruction is probably the reason for the generalized haemochromatosis followed by fibrosis and the complete picture of haemochromatosis. Treatment by transfusion or splenectomy causes only slight improvement and hastens the process of haemochromatosis. Thrombotic complications often follow splenectomy. Pyridoxine produces marked haematological improvement in some patients, but only partial improvement in others. It has been noted that the increased erythropoiesis increases the folic acid requirements, so that the administration of folic acid may be useful adjuvant therapy. As the termination of the disease is hastened by the development and progression of the haemochromatosis, the authors consider that repeated venesection deserves an important place in treatment, especially in patients who are pyridoxine-sensitive.

R. F. Jennison

1053. **Antibody to Intrinsic Factor in Serum from Patients with Pernicious Anaemia**

G. H. JEFFRIES, D. W. HOSKINS, and M. H. SLEISINGER. *Journal of Clinical Investigation* [J. clin. Invest.] 41, 1106-1115, May, 1962. 8 figs., 19 refs.

The authors describe a series of experiments carried out at New York Hospital-Cornell Medical Center to define the interaction of pernicious-anaemia sera and human intrinsic factor both *in vivo* and *in vitro*. The blocking action of certain pernicious-anaemia sera on intrinsic-factor activity was demonstrated by vitamin-B₁₂ absorption tests in which mixtures of serum with intrinsic factor and vitamin B₁₂ labelled with ⁶⁰Co (⁶⁰CoB₁₂) were fed to patients with pernicious anaemia. Such an intrinsic-factor antibody was demonstrated in 9 patients with pernicious anaemia and in one with atrophic gastritis; it was not found in 11 other patients with pernicious anaemia. The interaction *in vitro* of sera and intrinsic factor was studied by electrophoretic and immunological techniques. It was found that those pernicious-anaemia sera that inhibited intrinsic-factor activity in absorption studies contained γ -globulin which combined with human intrinsic factor-⁶⁰CoB₁₂ complex. The authors have not been able to determine the mechanism by which γ -globulin of inhibitory sera prevents absorption of vitamin B₁₂. Inhibition occurs only when the blocking γ -globulin is present in the gastro-intestinal lumen. They discuss the significance of this intrinsic-factor antibody in relation to the aetiology of pernicious anaemia.

Janet Vaughan

NEOPLASTIC DISEASES

1054. **The Role of Corticosteroids in the Treatment of Malignant Lymphomas**

S. KOFMAN, C. P. PERLIA, E. BOESEN, R. EISENSTEIN, and S. G. TAYLOR III. *Cancer* [Cancer (Philad.)] 15, 338-345, March-April, 1962. 4 figs., 34 refs.

This is a report from the Presbyterian-St. Luke's Hospital, Chicago, of 53 patients with malignant lymphomata treated with corticosteroids. The cases were classified histologically into 4 groups: (1) Hodgkin's disease; (2) lymphosarcoma; (3) reticulum-cell sarcoma; and (4) malignant lymphoma, giant follicular type. Chronic lymphatic leukaemia was not included in the classification. Of the 53 patients, 20 were in an advanced stage of the disease and were refractory

to treatment with radiation and/or alkylating agents; 36 were given prednisolone, and the other 17 prednisolone and chlorambucil. A variety of dosage schedules were adopted for initial and maintenance therapy.

Regression occurred in 28 patients (53%), and the disease remained controlled in 10 patients at the time of writing. The longest regression following treatment with corticosteroids alone continued after 4 years in a patient with lymphosarcoma. The side-effects that limited therapy most frequently in this study were gastric and duodenal ulcers, infections, and increased nervousness.

It is concluded that corticosteroids have a definite place in the therapy of malignant lymphomata, particularly in patients who are refractory to other forms of treatment.

A. W. H. Föxell

1055 (a). **The Chemical Pathology of Hodgkin's Disease.** (Contribuição para o estudo da patologia química da doença de Hodgkin)

F. J. Z. C. CHAVES, S. F. GOMES DA COSTA, and J. A. FILIPE DA SILVA. *Gazeta médica portuguesa [Gaz. méd. port.]* 15, 16-26, Jan.-Feb. [received July] 1962. 7 figs., 19 refs.

1055 (b). **The Chemical Pathology of Reticulosarcoma.** (Contribuição para o estudo da patologia química dos reticulo-sarcomas)

E. V. M. CRESPO, S. F. GOMES DA COSTA, and J. A. FILIPE DA SILVA. *Gazeta médica portuguesa [Gaz. méd. port.]* 15, 26-32, Jan.-Feb. [received July], 1962. 2 figs., 10 refs.

1055 (c). **The Chemical Pathology of the Leukaemias.** (Contribuição para o estudo da patologia química das leucemias)

S. F. GOMES DA COSTA, F. J. Z. C. CHAVES, J. A. FILIPE DA SILVA, and E. V. M. CRESPO. *Gazeta médica portuguesa [Gaz. méd. port.]* 15, 33-43, Jan.-Feb. [received July], 1962. 7 figs., 13 refs.

These three papers from the University of Lisbon deal with some aspects of the chemical pathology of certain malignant conditions. The authors found in previous experiments that when they tested the sera of patients with Hodgkin's disease by immunoelectrophoresis using specific antisera and by paper electrophoresis, an irregular precipitation line appeared in 4 out of every 5 cases. This was called the H-line and was closely associated with the α_2 -C line. When they attempted to isolate the abnormal protein from 3 patients, two abnormal protein fractions were isolated by adsorption in one but none was isolated in the others, although an abnormal line was seen in the α_2 region in 2. However, 2 of the patients had been treated by blood transfusion and nitrogen mustard some days before, and it is not known how this might have affected the results. The authors consider, however, that these abnormal lines may be interpreted as changes of a quantitative nature.

Paper electrophoresis and immunoelectrophoresis were carried out in 3 cases of reticulosarcoma, blood being taken before any treatment and the corresponding specific antisera being used. No abnormal protein was demonstrated. There was reduction in albumin and an increase in α_2 - and γ -globulins, but no significant change in the excretion of amino or organic acids in the urine was detected.

Similar tests were performed on one case of acute lymphatic leukaemia, one of chronic myeloid-leukaemia, and one of chronic lymphatic leukaemia. Nothing abnormal was found in the first 2, but an abnormal protein was

demonstrated in the serum of the patient with chronic lymphatic leukaemia. The authors are carrying out experiments on the urinary excretion of amino acids and acids of the Krebs cycle with a view to finding a test which might be called the "organoaciduria" test and which might throw light on the pathogenesis of pathological aminoaciduria.

W. K. Dunscombe

1056. **Therapy of Acute Leukaemia: Comparison of Initial Treatment with 6-Mercaptopurine Alone and in Combination with Steroids**

J. M. BRIDGES, D. M. HAYES, and M. G. NELSON. *British Journal of Cancer [Brit. J. Cancer]* 16, 46-55, March [received June], 1962. 22 refs.

The value of 6-mercaptopurine alone and in combination with corticosteroids in the treatment of acute leukaemia was studied at the Royal Victoria Hospital, Belfast, in 50 adult patients aged 15 to 77 years. The leukaemia was classified as monoblastic in 21 patients, myeloblastic in 10, lymphoblastic in 10, and undifferentiated stem-cell in 9. In 14 patients, 9 of whom failed to respond, the initial treatment was with 6-mercaptopurine alone in a dosage of 2.5 mg. per kg. body weight daily for 4 to 6 weeks, to a total dose of 6 to 8 g. No general toxic effects and no untoward depression of the bone marrow were observed. The mean survival time of the whole group was 4.3 months, but the group included an undue proportion of patients with resistant monoblastic leukaemia. In 3 cases in which there was an initial complete remission the mean survival time was 11 months.

Mercaptopurine and a corticosteroid were given to 36 patients; the dosage of the latter, usually prednisone, was 60 to 100 mg. daily, which was reduced after 2 weeks. Of the 36 patients, 12 had a complete remission lasting an average of 6.3 months, 11 had a partial remission, and 13 failed to respond. It is pointed out that corticosteroids cause side-effects such as Cushingoid facies, glycosuria (in 7 patients in the series); and myopathy. They also predispose to infections, varying from oral moniliasis to fatal septicaemia (7 cases), and to death from haemorrhage (21 of the 36 patients "died as a direct result of uncontrollable haemorrhage").

It is concluded that 6-mercaptopurine is the initial drug of choice in all adult cases of acute leukaemia, even though the results appeared to be better with the combined therapy. However, the side-effects of corticosteroids outweigh the advantages (the response is usually apparent in 10 days as against 2 to 4 weeks with 6-mercaptopurine alone). Corticosteroids, although of undoubted value, should be given only when an immediate response is desired or when there is resistance to 6-mercaptopurine. In monoblastic leukaemia the addition of corticosteroids is of no value.

R. B. Thompson

1057. **A Clinical and Pathological Study of Resistance to Infection in Chronic Lymphatic Leukemia**

D. G. MILLER, J. M. BUDINGER, and D. A. KARNOFSKY. *Cancer [Cancer (Philad.)]* 15, 307-329, March-April, 1962. 7 figs., 18 refs.

This paper presents a study of 11 patients with chronic lymphatic leukaemia the course of which was complicated by recurrent infections. In each case the entire course of the disease was analysed from diagnosis to death. Pulmonary infections predominated, the most common infecting

organisms being *Staphylococcus aureus* and pneumococci. The cellular response to inflammation consisted primarily of granulocytes, and these were the predominant cells found in the sputa of 8 patients during pneumonia. Five of the 7 patients examined post mortem showed an abundant polymorphonuclear response in the areas of infection; unusual giant pleomorphic eosinophilic reticulum cells were found in 3 patients.

In every case, when the leukaemia became worse the infection also became worse. In some instances treatment of the disease had a favourable effect on the infectious complications. All patients had a low or border-line γ -globulin level attributable to the leukaemia. There was some evidence that additional benefit was obtained by the administration of γ -globulin with antibiotics for the treatment of infections, while antibiotics alone may be effective for long periods. Oral phenoxymethylpenicillin was the first choice, and tetracycline the second. The dosage of γ -globulin was 0.3 ml. per lb. (0.66 ml. per kg.) body weight initially, followed by 0.15 ml. per lb. (0.33 ml. per kg.) every 2 weeks. In no case did the γ -globulin return to normal levels.

The authors stress the treacherous nature of the infectious processes in these patients. The onset of a seemingly minor attack of bronchitis was a major danger sign demanding vigorous treatment to impede its progression into bronchiectasis or pneumonia.

A. W. H. Foxell

1058. **The Quantitative Relation between Platelet Count and Hemorrhage in Patients with Acute Leukemia**

L. A. GAYDOS, E. J. FREIREICH, and N. MANTEL. *New England Journal of Medicine* [New Engl. J. Med.] 266, 905-909, May 3, 1962. 5 figs., 21 refs.

Thrombocytopenia is accepted as the most important single factor in the genesis of haemorrhage occurring in patients with acute leukaemia, although in a few cases hypofibrinogenaemia, fibrinolysis, qualitative platelet defects, and capillary damage may play a part. The relationship between the platelet level and the occurrence of haemorrhage is poorly defined. At the National Cancer Institute, Bethesda, Maryland, 92 patients (40 adults and 52 children) with acute leukaemia were studied from before the institution of chemotherapy until 85 had died. Acute myelogenous leukaemia is said to have accounted for 34 cases and acute lymphocytic leukaemia for 57 cases; only one case was unclassified.

Platelet counting was carried out thrice weekly on in-patients and once every 2 or 3 weeks on out-patients. With the method employed (Bretner *et al.*, *Amer. J. clin. Path.*, 1953, 23, 15; *Abstr. Wld Med.*, 1953, 14, 178) normal counts fell in the range 150,000 to 450,000 per c.mm. When the number of patient-days on which there was clinical evidence of haemorrhage was plotted against the platelet levels no definite threshold value was found, but haemorrhages were noted on 92% of the days on which platelet counts were 1,000 per c.mm. or less, but on only 8% of days on which counts were between 50,000 and 100,000 per c.mm. Gross haemorrhage, such as obvious haematuria, melaena, or haematemesis, was uncommon with platelet counts above 20,000 per c.mm. These relationships between platelet counts and the occurrence of haemorrhage were obvious even when the cases were analysed by age and morphological type of leukaemia, and when account was taken of therapeutically induced remissions in the disease. In individual

cases a falling platelet count was noted to precede an episode of gross haemorrhage. Fatal intracranial haemorrhage occurred in 16 patients, and in 8 of these haemorrhage was associated with blastic crises; at necropsy intracerebral leukaemic nodules and more diffuse infiltration were found. In this group of patients platelet levels were relatively high.

The authors discuss the interpretation of these observations and conclude that they fit best a state where a low platelet count is not by itself responsible for haemorrhage, but only when it is coupled with precipitating events which would not cause haemorrhage in the absence of thrombocytopenia.

A. G. Baikie

1059. **Leukemia in Man following Exposure to Ionizing Radiation: a Summary of the Findings in Hiroshima and Nagasaki, and a Comparison with Other Human Experience**

A. B. BRILL, M. TOMONAGA, and R. M. HEYSSEL. *Annals of Internal Medicine* [Ann. Intern. Med.] 56, 590-609, April, 1962. 4 figs., bibliography.

The complex methods used in this survey by the Atomic Bomb Casualty Commission, Hiroshima, have been previously described and are therefore only summarized in this paper. Evidence is presented that the incidence of leukaemia is greatly increased in the survivors exposed less than 1,500 metres from the hypocentre of the nuclear explosions at both Hiroshima and Nagasaki. At Hiroshima the incidence at over 2,000 metres is not significantly greater than that expected in Japan as a whole—some 20 to 30 cases per million per year. In a similar area at Nagasaki, however, there is a significant ($P < 0.05$) but unexplained increased incidence. At Hiroshima a uranium bomb was used; exploded, whereas at Nagasaki a plutonium bomb was used; these have different emissions of gamma-rays and neutrons and this may have had some influence in determining the incidence of leukaemia. Some differences in incidence in the two cities probably arose artificially and may well have been partly due to shielding. In Nagasaki, for instance, the hypocentre covered relatively few residences; here the incidence in females was approximately 3 times the expected rate, while in males it was 8 times the expected rate. In Hiroshima the sex incidence is approximately equal. Combined figures for both cities indicate ($P < 0.05$) that the greatest increase in incidence was in those under the age of 10 years at the time of exposure. There was a markedly increased incidence of acute lymphoblastic leukaemia, but it is also of interest that 5 cases of chronic granulocytic leukaemia occurred between the ages of 0 and 9 years. The incidence is, however, higher than expected for all types of leukaemia in each age group. It is remarked that an initial pancytopenia was not noted in these cases.

The increase in incidence seems to have started about 14 years after exposure; the greatest number of cases occurred between 1950 and 1952, since when the numbers have fallen, although they are still well above the expected value. The incidence has been much higher in those who had suffered from acute radiation sickness than in those who had not. The relationship of leukaemia incidence to dose of mixed gamma and neutron radiation (so far as this can be assessed) appears to be linear. If a threshold exists, it appears to be less than 80 rads.

The authors conclude that an increased incidence is to be expected over 14 years after exposure and that an average of 1 to 2 cases per rad per year are to be expected during that period.

R. B. Thompson

Respiratory System

1060. The Aetiology and Treatment of Epistaxis: Based on a Review of 200 Cases

J. EVANS. *Journal of Laryngology and Otology* [J. Laryng.] 76, 185-191, March [received May], 1962. 11 refs.

The author of this paper from the Royal Infirmary, Blackburn, does not agree that the causes of epistaxis can be classified as (1) hypertension or arterial disease; (2) local nasal disease; and (3) haemorrhagic disease. He considers that most cases of epistaxis are primarily infective in origin. He found infection in the upper respiratory tract or sinuses in no less than 88% of his 200 patients of all ages. [It seems more likely that infection may have been only a precipitating or contributory cause in many of the cases mentioned in this paper.]

Search for the cause of epistaxis requires a broad outlook for such conditions as general infections, cardiac and vascular disease, endocrine disturbances, other evidence of haemorrhagic disease, and nephritis as well as the investigation of local causes. Long-term therapy may require the treatment of any of these conditions.

Packing the nose should be as localized and as atraumatic as possible, especially in cases of haemorrhagic disease. In elderly and arteriosclerotic patients sedation with "omnopon" is important. In severe traumatic bleeding from above the middle turbinal, ligation of the anterior ethmoidal artery in the medial wall of the orbit should be carried out; if such bleeding comes from the middle turbinal or below it, ligation of the sphenopalatine artery by the transantral approach can be performed: there were 2 such cases in the present series. Equally effective in these latter cases is ligation of the external carotid artery.

The 2 deaths in the series were due respectively to multiple familial telangiectasis and to heart failure in a hypertensive subject.

Norman W. MacKeith

LUNGS AND BRONCHI

1061. A Study of Respiratory Function in Post-embolic Cor Pulmonale. (Étude de la fonction respiratoire dans le cœur pulmonaire chronique post-embolique)

P. SADOUL, G. FAIVRE, J. M. GILGENKRANTZ, F. CHERRIER, and C. SAUNIER. *Journal français de médecine et chirurgie thoraciques* [J. franç. Méd. Chir. thor.] 16, 433-446, May-June, 1962. 6 figs., 29 refs.

The authors, from the University of Nancy, report on 4 men, aged 46, 47, 48, and 50 years respectively, all of whom had progressive severe dyspnoea after transient haemoptysis following leg vein thrombosis. Radiographic, electrocardiographic, and respiratory function findings are given for all 4 patients, and the results of cardiac catheterization for 3.

The constant characteristic functional finding in these patients, in whom the clinical diagnosis was hardly in doubt and in 3 of whom the right ventricular pressure was raised, was hyperventilation associated with an increased physiological dead space. There was little change in vital capacity, forced expiratory volume or residual capacity, although the

ratio forced expiratory volume:vital capacity was slightly reduced in 2 patients. In all 4 cases the arterial pCO_2 was below 33 mm. Hg, and plotting the arterial carbon dioxide and pH-readings on a Davenport diagram showed the presence of a partly compensated respiratory alkalosis. In spite of the hyperventilation, the arterial oxygen saturation was reduced in 2 patients and they had an increased alveolo-arterial gradient for oxygen (35 and 42 mm. Hg respectively).

The authors agree with other workers that this hypoxia is difficult to explain and discuss the possibility of shunts, ventilation-perfusion imbalance, and defects of diffusion. They consider that the functional findings of increased alveolar ventilation and enlarged physiological dead space are an aid to the diagnosis of chronic postembolic cor pulmonale.

P. Hugh-Jones

1062. The Hypoxic Drive in Respiratory Failure

R. W. B. PENMAN. *Clinical Science* [Clin. Sci.] 22, 155-160, April, 1962. 2 figs., 20 refs.

Administration of oxygen to patients with respiratory failure is known to reduce pulmonary ventilation. This effect has been attributed to depression by oxygen of a peripheral chemoreceptor "hypoxic drive", but this mechanism has recently been questioned. At the Department of Therapeutics, Queen's University, Belfast, the author therefore studied the effect on 13 patients with respiratory failure of breathing 100% oxygen for 10 minutes. Oxygen breathing depressed ventilation and increased arterial carbon dioxide tension. Statistical analysis revealed that the change in ventilation after oxygen inhalation depended largely on the initial pH of the arterial blood rather than its oxygen content. When the initial blood pH was higher than 7.37 there was a large rise in carbon dioxide tension (that is, ventilation) after breathing oxygen, but when the pH was below 7.37 oxygen administration caused only a small rise in arterial carbon dioxide tension, and also therefore in ventilation. The results indicate that when patients with respiratory failure are acidaemic the decrease in pulmonary ventilation on breathing oxygen, which can be attributed to depression of a "hypoxic drive", is negligible.

Bernard Isaacs

1063. Pulmonary Infarction. Clinical Results of Treatment with Thrombolytic Drugs. (Infarto polmonare. Risultati clinici di diversi tipi di trattamento trombolitico)

R. TURPINI. *Giornale di gerontologia* [G. Geront.] 10, 239-250, March [received June], 1962. 15 figs., 13 refs.

In this paper from the University of Pavia, Italy, the author describes the treatment of 14 cases of pulmonary infarction. One patient was given plasmin, 5 were given a combination of trypsin and heparin, 5 nicotinic acid, and 3 bacterial pyrogens. The average time required for improvement (assessed in terms of regression of symptoms and stay in hospital) in the patients treated with trypsin-heparin was 90 hours, in those treated with nicotinic acid it was 35 hours, and in those treated with bacterial pyrogens 38 hours. Thus,

preparations which activate fibrinolysis seem to be more effective than those which have a direct fibrinolytic action. The latter are inactivated by human plasma before they can exert their action on clots. Indirect fibrinolytics, on the other hand, activate natural fibrinolysis and thus promote endogenous thrombolysis. The author considers, however, that a larger series of cases must be treated and analysed before a definite conclusion can be reached.

Arnold Pines

1064. Bronchiolar Behavior in Pulmonary Emphysema and in Bronchiectasis

J. K. ISLEY JR., J. BACOS, J. B. HICKAM, and G. J. BAYLIN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 853-853, May, 1962. 3 figs., 13 refs.

Bronchography was performed on 54 patients at Duke University Medical Center, Durham, North Carolina, to observe the behaviour of the bronchioles in both normal and diseased conditions. The medium used was "dionosil oily", a propylidone suspension. All patients were conscious, but had received premedication and a local anaesthetic. Films were exposed during normal inspiration and expiration and during forced expiration.

In 21 patients with normal bronchioles there was a 10 to 20% decrease in bronchiolar calibre during normal expiration and a further decrease up to 30% on forced expiration. In 13 cases of bronchiectasis more marked changes in bronchiolar calibre occurred during the respiratory cycle, and the bronchioles were wider than normal at all times.

The bronchioles in 12 patients with generalized primary emphysema were larger than normal during inspiration, but narrowed markedly during expiration and still further during forced expiration. The changes in calibre of the bronchioles in 7 cases of compensatory emphysema were within normal limits.

The possible mechanism of these changes is discussed, and it is suggested that the major defect in primary emphysema is loss of rigidity of the bronchiolar walls.

D. Goldman

1065. The Cytology and Histochemistry of Sputum Cells. I. Preliminary Differential Counts in Chronic Bronchitis

S. CHODOSH, C. W. ZACCHEO, and M. S. SEGAL. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 635-648, May, 1962. 28 refs.

This is a preliminary report from the Boston City Hospital of a careful investigation of the sputum cytology in cases of chronic bronchitis.

The patients were divided into three groups as follows: (1) those who were in a stable state without acute inflammatory exacerbation; (2) those in an acute inflammatory state; and (3) a subdivision of the first group—those who had polycythaemia. In all specimens the neutrophil granulocyte was the predominant cell type; bronchial epithelial cells were the next most frequent, and histiocytes the third in frequency. Eosinophil granulocytes were relatively uncommon. In the cases with acute inflammation there was a great increase in the rate of daily production of cells of all types (calculated by multiplying the cell count by the sputum volume); the greatest increase in these episodes being due to neutrophil granulocytes. There was an increased secretion of all types of bronchial epithelial cells.

The group of cases with secondary polycythaemia (studied

separately as representing a specific type of cellular reaction in the blood) differed from the others only in that they had a higher frequency of cellular inclusions within the histiocytes.

Although there was a wide range in all cell counts within each group of patients, the authors state that within a single patient the distribution of cells tends to be relatively stable from day to day, so that changes may be of clinical significance. They express the hope that "continued correlation of the clinical status of the patient with the quantitative cellular response noted in the sputum will provide more insight into the pathogenesis and etiology of chronic bronchitis and other bronchopulmonary diseases".

C. M. Fletcher

1066. Pulmonary Fungal Infections Simulating and Misdiagnosed as Other Diseases

E. W. CHICK. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 702-707, May, 1962. 7 figs., 5 refs.

The author points out the growing importance of fungal infections; for instance, it is estimated that 500,000 new cases of histoplasmosis occur annually in the U.S.A. and that about 10 million people have been infected with coccidioidomycosis. No information is available as to the incidence of blastomycosis, cryptococcosis, actinomycosis, and nocardiosis, partly because there is no satisfactory antigenic test. Then there are the "opportunistic" infections in which fungi, normally saprophytic, become pathogenic in debilitated subjects or in those receiving broad-spectrum antibiotics or corticosteroids. These fungi include *Aspergillus*, *Candida*, and *Mucor*. Diagnosis may not be easy because the clinical and radiological features resemble those of commoner diseases; also the one essential basis for diagnosis, culture of the organism, may be difficult to achieve or, with a common fungus like *Aspergillus*, its significance may be difficult to establish.

To illustrate his points the author describes 7 cases seen at the Veterans Administration Hospital, Durham, North Carolina. All were in males aged 13 to 70. Three had an illness resembling pulmonary tuberculosis, which proved to be due to blastomycosis in 2 and histoplasmosis in one. There were 2 more cases of histoplasmosis, one resembling sarcoidosis and the other a pulmonary metastasis. The 2 "opportunistic" infections both suggested a pneumonia; one, in an elderly diabetic, was due to *Nocardia*, and the other, in a patient with myelofibrosis, to *Mucor*.

Arthur Willcox

1067. Carcinoma of the Lung: Review of 509 Cases

M. S. SABOUR, L. M. OSMAN, J. GLEN, T. FAHY, and P. LAMB. *Diseases of the Chest* [Dis. Chest] 41, 530-546, May, 1962. 8 figs., 7 refs.

The authors review 396 cases of carcinoma of the lung admitted to Springfield Hospital, Grimsby, England, between 1952 and 1960, and 113 admitted to Ain-Shams University Hospital, Cairo, Egypt, between 1954 and 1958. [The sources of the cases and the degree of selection are not made clear; and it is not apparent why these two obviously dissimilar groups are treated together.] Of the larger (English) group, squamous-celled carcinoma formed 68%, but of the smaller (Egyptian) group, only 44%. [No other data are given separately for the two national groups.] The ratio of men to women was 9 to 1; two-thirds of the

tumours were central in position, 18% intermediate, and 14% peripheral or subpleural. Mass radiography was responsible for the diagnosis in 8% of the patients; these had no chest symptoms. The initial symptoms and physical signs and the x-ray findings are reviewed. Of confirmatory methods of diagnosis, needle biopsy proved most useful, the findings being positive in 115 of the 131 patients on whom it was performed; bronchoscopy, bronchoscopy biopsy, and sputum cytology (207 positives in 509 patients) were also valuable; tomography and scalene-node biopsy were seldom helpful.

The number of patients subjected to surgery was 170 (33%). In the remainder the condition was considered inoperable, because of spread of growth, distant metastases, or the patient's poor general condition; the reasons are set out in detail. Resection was possible in 111 patients (22% of the entire series); there were 68 pneumonectomies, 40 lobectomies, and 3 pleuropneumonectomies. Radiotherapy was given to 179 patients. In 60 cases the radiotherapy is described as "radical"; these patients had undifferentiated-cell carcinoma but no evidence of distant metastases. [No details of radiotherapy are given.] The remainder of the irradiated group had palliative courses only to relieve specific symptoms such as intractable cough, pain, haemoptysis, dyspnoea, dysphagia, or superior vena caval obstruction. Only one of this group of 119 patients who received palliative radiotherapy is alive after 4 years. Patients with distant metastases and undifferentiated-cell growths were treated by the antimitotic drugs nitrogen mustard (37 patients) and triethylene melamine (6 patients).

Of the patients treated by resection, 62% were alive after one year and 19% after 5 years. Of those treated by radical radiotherapy, 98% were alive after one year, but only 5% after 5 years. There were no 5-year survivors among the 119 patients who had palliative radiation therapy. Chemotherapy was considered to be of little value in palliation, since, with the possible exception of superior vena caval obstruction, symptoms were more effectively relieved by radiotherapy.

E. Stanley Lee

1068. Carcinoma of the Lung: an Analysis of 362 Cases Diagnosed and Treated in One Year

J. C. W. MACFARLANE, B. J. DOUGHTY, and W. A. CROSBIE. *British Journal of Diseases of the Chest* [Brit. J. Dis. Chest] 56, 57-63, April, 1962. 5 figs., 4 refs.

The authors describe 362 patients in whom carcinoma of the lung was diagnosed at the London Chest Hospital during 1960. The patients were admitted consecutively, but were "selected" in the sense that many had been referred by chest clinics solely with a view to surgery.

Of the 362 patients, 76% were aged between 50 and 70 and 337 were males. The sex ratio was thus 13.5:1 for the whole series, but varied in the different histological types from (males to females) 46.3:1 for squamous-celled carcinoma to 3.6:1 for the oat-cell type. The number of cases considered to be inoperable was 175 (48%) and the percentage operated upon varied with the type of tumour (71% of all adenocarcinomata as compared with 22% of tumours of the oat-cell type). The most common initial symptoms were haemoptysis, cough, breathlessness, pain in the chest, and loss of weight. In 14 of the patients (4% of the total), in whom the new growth had been discovered during mass radiography, there were no symptoms. Symptoms had

been present for less than 6 months in 73% of the patients and most of the inoperable cases proved fatal within one year of the onset of symptoms. No association between lung cancer and any one blood group was detected. In 80% of the patients the sputum was examined for malignant cells, and these were found in 37% of this group. Malignant cells were found in the sputum of 53% of the patients with squamous-celled carcinoma whose sputum was examined, and in the sputum of only 27% of those with adenocarcinoma.

Of the 166 patients considered unfit for operation, only 14 were still alive when the report was written, and of these all but 2 ("unconfirmed" cases) were slowly deteriorating. The survival time was not affected by thoracotomy, administration of nitrogen mustard, or radiotherapy. The average survival time of the patients not treated was 5.9 months, of those given nitrogen mustard 7.4 months, and of those given radiotherapy 8.7 months. The authors state that the numbers in the last two groups are too small for statistical evaluation. The 184 patients operated on are divided into 2 groups, 80 in whom lobectomy was performed and 104 who underwent pneumonectomy. In the lobectomy group 42 patients (53%) had survived for 24 months; the addition of nitrogen mustard or x-ray therapy to lobectomy did not alter the survival period; the average survival period of the remaining patients was just over 7 months. Of the 104 patients who underwent pneumonectomy, 55 (53%) had survived for 2 years; the average survival time of those who died was 6.2 months, but where nitrogen mustard was given after operation it was 7.2 months and where radiotherapy followed operation it was 9.8 months.

[This paper should be studied in conjunction with that on the treatment of inoperable carcinoma of the lung with vinblastine sulphate (see Abstract 1069).]

J. Warwick Buckler

1069. The Treatment of Inoperable Carcinoma of the Lung by Vinblastine Sulphate: a Preliminary Report

J. C. W. MACFARLANE, B. J. DOUGHTY, and W. A. CROSBIE. *British Journal of Diseases of the Chest* [Brit. J. Dis. Chest] 56, 64-69, April, 1962. 1 fig., 6 refs.

The authors report the results in 25 cases of carcinoma of the lung treated at the London Chest Hospital with the oncolytic drug vinblastine sulphate, which is an alkaloid extracted from the leaves of the flowering herb periwinkle, *Vinca rosea* Linn. There were 22 males and 3 females. The disease was in an advanced stage and was considered to be inoperable. The histological diagnosis was adenocarcinoma in 4 cases, oat-cell tumour in 2, squamous-cell tumour in 8, and undifferentiated-cell tumour in 6, while in the remaining 5 the diagnosis was regarded as "unconfirmed" although the clinical and radiological evidence placed it beyond doubt. The drug was given intravenously in weekly doses of 0.1 to 0.25 mg. per kg. body weight.

At the time of the report the results were as follows: 5 patients had died within one month of beginning treatment; 5 patients had refused further treatment or to attend for further examination; of 6 who had been on treatment for 4 months, one had died and the others were alive and well; of 9 who had been on treatment for 9 months, 6 were well, 2 were deteriorating rapidly, and one had died after 9 months. The average survival time for these patients was 7.5 months, even if it was assumed that all (excluding the defaulters) were dead. The subjective improvement felt by

the surviving patients had not been accompanied by a significant change in the radiological appearances, although there was demonstrable shrinkage of the lung shadow in 3 cases treated for over 6 months. Necropsy was not authorized for any of the 7 patients who died during treatment. Side-effects were minimal and were overshadowed by the euphoria produced by the drug. Slight anorexia was reported by 2 patients, and all but 3 complained of a peculiar taste in the mouth.

The authors conclude that vinblastine sulphate therapy is an advance on other adjuvant treatment, but that further experience is necessary to determine the dosage; this at present is controlled chiefly by the leucocyte count, which must be repeatedly determined. *J. Warwick Buckler*

1070. Lung-cancer Mortality as Related to Residence and Smoking Histories. I. White Males

W. HAENSZEL, D. B. LOVELAND, and M. G. SIRKEN. *Journal of the National Cancer Institute [J. nat. Cancer Inst.]* 28, 947-1001, April, 1962. 2 figs., bibliography.

In this study at the National Cancer Institute, Bethesda, Maryland, and the National Vital Statistics Division, Washington, residential and smoking histories were collected for a 10% sample of white males certified as dying of lung cancer in the U.S.A. in 1958. The information was obtained by sending questionnaires to persons who had informed about the fact of death; additional information about the validity of the diagnosis was supplied by the certifying physicians.

Altogether 2,553 deaths were selected; 57 were excluded because the physician changed the diagnosis and 115 were excluded for other reasons. Detailed information was obtained about 2,191 (92%) of the remainder. Corresponding information for a representative sample of the population was provided by histories obtained from 31,516 white males aged 35 years and over, as part of the U.S. Bureau of the Census population survey. The results in relation to smoking and lung cancer are similar to those found in other studies in the U.S.A. In this paper they are expressed in the form of standardized mortality ratios (S.M.R.)—that is, as percentages of the mortality in the whole population standardized for age. For lifelong non-smokers the S.M.R. was 16; for men who regularly smoked cigarettes at the rate of one packet [presumably containing 20 cigarettes] or less per day it was 125; and for men who smoked more than one packet per day it was 501.

S.M.R.s for men resident in urban and in rural areas were respectively 119 and 73, so that the urban:rural ratio was 1.63:1, but when the comparison was between men who had lived all their lives in the areas the ratio was 2.51:1. When the S.M.R.s were also standardized for smoking history these ratios were reduced to 1.43:1 and 2.00:1 respectively. Differences in smoking habits before death were, therefore, insufficient to account for the differences in the urban and rural rates. When non-smokers alone were concerned the S.M.R.s were low in all areas and showed only trivial differences.

In all residential groups there was a steady increase in mortality with the amount smoked, but the increase was generally greater for men who had lived in large towns than for men who had lived wholly in the country. The joint effect of urban residence and smoking was greater than would be expected on the assumption that there were two separate

risks which could be added; the data fitted better the hypothesis that the risks multiplied one another. One unexpected finding was that the rates were higher among men who had migrated to large towns than among those who had resided there all their lives. For example, the S.M.R. for men resident and born in towns of over 500,000 population was 119; for residents in such towns who were born abroad it was 144, and for those who were born on farms 149. This finding of a higher rate among men who had migrated to towns from farms was maintained for all types of community; but it was not found among the control data obtained for men dying with cancer of the colon and rectum. This evidence, taken in conjunction with that from other countries, suggests that migrants form a special group with a high risk of lung cancer.

One possible explanation is that lifetime residents in large towns become adapted to exposure to pollution, whereas abrupt contact with matter from the urban atmosphere may inhibit the action of the respiratory cilia and so permit longer contact with any carcinogens. *Richard Doll*

1071. Angiography as a Means of Determining Resectability of Primary Lung Cancer

D. E. SANDERS, N. C. DELARUE, and G. LAU. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine [Amer. J. Roentgenol.]* 87, 884-891, May, 1962, 11 figs., 20 refs.

Angiographic examination of the heart and great vessels to determine local extension of lung cancer was carried out on 100 pathologically proven cases in the Departments of Radiology and of Surgery, University of Toronto. The technique was as follows. A No. 10 end-opening Lehman catheter was placed in the innominate vein or proximal superior vena cava, and 55 ml. of contrast medium was injected by a Gidlund syringe at a pressure of 5 to 7 kg. per sq. cm. Simultaneous biplane exposures were obtained at 2 films per second for 5 seconds, followed by one film per second for 5 seconds. The procedure was employed only in patients with hilar or mediastinal lesions after other intensive investigations were complete, as a normal angiogram does not exclude extension remote from the heart and great vessels. The angiographic criteria for non-resectability included any persistent filling defect or narrowing of the superior vena cava or the right or left atrium; involvement proximal to the bifurcation of the right pulmonary artery, or within the proximal 1.5 cm. of the left pulmonary artery, or within the terminal 1 to 2 cm. of the four major pulmonary veins. (These can be filled by reflux from the left atrium when the pulmonary artery on the side of the reflux is occluded.)

Of the 100 patients, in only 42 were the lesions considered resectable, of whom, because of other disability, only 32 proved suitable for thoracotomy. In 29 the absence of involvement of the heart and great vessels was confirmed. In the remaining 3 the involvement, not recognized preoperatively, arose from carcinoma of the left upper-lobe bronchus and was in the posterior aspect of the left lung root.

Of 52 patients with angiographically non-resectable disease, thoracotomy was carried out in 18. In 17 the findings proved correct, and no excision could be attempted. In one a successful pneumonectomy was performed after a course of cobalt beam therapy, but the patient died six months later. *B. Golberg*

Urogenital System

1072. Treatment of Balanitis Xerotica Obliterans with Hydrocortisone Injections

R. D. CATTERALL and J. K. OATES. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 38, 75-77, June, 1962. 1 fig., 7 refs.

Over a period of 5 years the authors have studied 41 cases of balanitis xerotica obliterans, which they consider to be a localized form of lichen sclerosus et atrophicus. Most of the patients were married and between 21 and 35 years of age. In 15 cases the patient sought advice because he feared he had a venereal disease; 23 patients had urethral discharge and 17 a history of recurrent non-gonococcal urethritis; 6 were found to have gonorrhoea. Twelve patients had urinary symptoms, and 2 of these presented with acute urinary retention. In all cases the sclerotic tissue affected the meatus; in 27 it was in the form of a white peri-meatal collar often extending into the fossa navicularis, and in 14 there was also sclerotic tissue on the glans. Six patients had plaques of lichen sclerosus et atrophicus elsewhere on the body. In 4 cases the meatal lesions disappeared spontaneously in 6 to 9 months, but in the remaining cases repeated attacks of urethritis and urinary-tract infections occurred.

Treatment in 21 cases was with 1 to 2 ml. of hydrocortisone acetate suspension injected once a week into the affected tissues after topical anaesthesia with a lignocaine jelly, 6 to 8 injections usually being required. Dilatation of the meatus was carried out after the injection. Improvement was recorded in 20 cases; 5 appeared to be completely cured, but in 5 others initial improvement was followed by relapse. In the one case which was not improved the condition progressed despite repeated injections. In the opinion of the authors, mild cases respond to regular dilatation alone.

P. T. Main

1073. Bacteriuria of Pregnancy: Relation to Socioeconomic Factors

M. TURCK, B. S. GOFFE, and R. G. PETERSDORF. *New England Journal of Medicine* [New Engl. J. Med.] 266, 857-860, April 26, 1962.

The authors, working at the University of Washington, determined the incidence of asymptomatic bacteriuria in pregnancy from catheter specimens taken from 1,727 women drawn from different hospital populations of varying social and financial status. Gram-negative organisms were isolated in significant numbers from 59 (3.4%) of the 1,727 women; these were: *Escherichia coli* in 46 cases, paracolon bacilli in 8 cases, *Klebsiella* in 2 cases, *Proteus mirabilis* in 2 cases, and mixed *Esch. coli* and *Klebsiella* in one case. Bacteriuria occurred in 6.5% of the low-income group and 2% of the middle-income group; in 8.6% of the negro women, but in only 2.7% of the white women; in 1.4% of the primigravidae, 2.7% of the women who had had from one to 3 previous pregnancies, and 5.4% of the women who had had 4 or more previous pregnancies. The incidence among multi-gravidae of low socio-economic status was 11.4%.

Arnold Pines

1074. Nil nocere!: Interstitial Nephritis Due to Abuse of Phenacetin. (Nil nocere!: Interstitiellé Nephritis und Phenacetinabusus)

W. SALOMON and A. SUFFAN. *Münchener medizinische Wochenschrift* [Munch. med. Wschr.] 104, 839-843, May 4, 1962. 8 figs., 11 refs.

The authors describe 7 cases of uraemia, probably due to phenacetin poisoning, seen at the Kaiser-Franz-Joseph Hospital, Vienna. The characteristic picture consisted of blood changes, papillary necrosis, and renal insufficiency, often with salt-losing nephritis. The blood changes included Heinz-body anaemia and verdohaemoglobin formation. Greyish cyanosis was often present. Hypertension was absent. The condition progressed even when phenacetin was stopped.

The authors conclude that the ingestion of phenacetin over long periods can be dangerous and wonder whether prolonged administration of other drugs may also have unexpected effects.

G. L. Asherson

1075. The Metabolic Defect Responsible for Uric Acid Stone Formation

P. H. HENNEMAN, S. WALLACH, and E. F. DEMPSEY. *Journal of Clinical Investigation* [J. clin. Invest.] 41, 537-542, March [received May], 1962. 5 figs., 16 refs.

Uric-acid renal stone formation may occur in hyperuricaemic, hyperuricemic gouty patients and those with chronic diarrhoea, but more often, in the experience of the authors, it is found in elderly Italian or Jewish patients without these abnormalities.

A study is reported in this paper from the Massachusetts General Hospital, Boston, of some of the chemical factors present in this last group of patients with normal serum and urinary uric acid levels. It was found that the average urinary pH was lower than in normal controls, and balance studies in 4 patients suggested decreased renal tubular secretion of ammonium. It is thought that deficient ammonium excretion is part of ageing, but when especially marked may contribute to uric-acid stone formation. In 10 of 18 patients with uric-acid stone formation unusually low urinary calcium levels were present in spite of normal serum calcium values, and this too, it is held, suggests disturbance of renal function. It is suggested that the higher incidence of uric-acid renal stones in Italian and Jewish patients points to the possibility of a congenital factor.

G. W. Csonka

1076. Critical Appraisal of the Renogram in Renal Vascular Disease

B. H. STEWART and T. P. HAYNIE. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 454-459, May 12, 1962. 5 figs., 7 refs.

Sixty-four patients with suspected renal hypertension were studied with I^{131} sodium *o*-iodohippurate ("hippuran") renograms, retrograde ureteral catheterization studies and arteriograms; occlusive renal vascular disease was found at operation in 20 patients. The renogram was

"correct" in 9 of 9 cases with unilateral main artery occlusion, in 4 of 6 cases of bilateral occlusive disease, and in 2 of 5 cases of segmental disease. A quantitative method of interpretation was superior to qualitative evaluation. The radioisotope renogram, by the present technique, was ineffective as a "screening" test of renal hypertension since false-negative results were noted with significant frequency in patients with correctable renal ischemia. It was useful, however, as one of several tests in the evaluation of hypertensive patients and in following patients after revascularization procedures.—[Authors' summary.]

1077. The Anatomical Basis and Dynamics of Vesicoureteral Reflux

F. D. STEPHENS and D. LENAGHAN. *Journal of Urology* [*J. Urol. (Baltimore)*] 87, 669-680, May, 1962. 8 figs., 19 refs.

Vesicoureteral reflux is an abnormal phenomenon. The concept of an intrinsic muscular valve which occludes the ureteric lumen by a longitudinal shearing action is regarded as the primary and essential mechanism governing one-way flow through the ureteric orifice. The combined effect of muscle action and hydrostatic pressure is an "activated" flap valve which is competent even against the severe "back pressures" of undoubted urethral obstruction.

Three kinds of anomaly were found to account for reflux-inducing impairment of this mechanism: (1) congenital absence of the submucosal segment, (2) wedge sector defects of the muscle, and (3) combinations of both these deformities. Similar anomalies co-existed when reflux was found in association with congenital organic urethral obstruction.

Vesicoureteral reflux was found to subside spontaneously in a high proportion of ureters studied over a 5- to 10-year period. Recovery is presumed to occur concomitantly with growth and strengthening of the meager muscular endowments of the abnormal submucosal segments. Reflux when uncomplicated by infection or urethral obstruction is harmless to the kidney and is not a factor in the causation of megaureter. Neither infection nor obstruction impairs the function of a normal ureterovesical valve but if the valve is weakened by congenital defects either may induce transient reflux while it prevails.

A corollary to the view that the muscle in the submucosal ureter is the essential activator of the sphincter mechanism, is that factors which impair its innervation may also cause reflux, and this possibility must be considered in paraplegic patients who so frequently exhibit reflux.—[Authors' summary.]

1078 Excretory Urographic Changes in Children which Suggest Occurrence of Reflux

F. C. MARSHALL. *Journal of Urology* [*J. Urol. (Baltimore)*] 87, 681-687, May, 1962. 8 figs., 2 refs.

This paper from the Columbia-Presbyterian Medical Center, New York, evaluates the use of intravenous pyelography as a screening test for vesico-ureteric reflux in children. Of 48 cases with reflux the intravenous pyelogram showed abnormality in all but 2; in 69 cases without reflux there were 33 normal pyelograms. It therefore appears to be rare for a normal pyelogram to be obtained in a child in whom reflux can be demonstrated; but the converse is not true. The abnormalities related to reflux included overfilling of the upper urinary tract when the bladder is full, and

pooling of contrast medium in redundant portions of a previously overstretched collecting system when the bladder is empty. D. A. K. Black

1079. The Causes of Vesicoureteral Reflux in Children

S. S. AMBROSE and W. P. NICOLSON III. *Journal of Urology* [*J. Urol. (Baltimore)*] 87, 688-694, May, 1962. 10 figs., 13 refs.

Vesicoureteral reflux is secondary to a variety of factors which alter the normal anatomical relationships of the ureter to bladder wall. Congenital ureteral ectopia lateralis with resulting loss of the intravesical ureter is the most common cause of reflux in children in our experience. This lesion alone may result in reflux or it may potentiate the effect of other factors such as lower urinary obstruction or neurogenic bladder disease. Lower urinary tract obstruction, neurogenic bladder disease, iatrogenic trauma, and local inflammatory disease of ureterovesical junction may result primarily in alterations at the ureterovesical junction sufficient to result in incompetence but are not the *sine qua non* of reflux.—[Authors' conclusions.]

1080. Acute Renal Failure after Open-heart Surgery Utilizing Extracorporeal Circulation and Total Body Perfusion: Analysis of One Thousand Patients

R. C. DOBERNECK, M. P. REISER, and C. W. LILLEHEI. *Journal of Thoracic and Cardiovascular Surgery* [*J. thorac. cardiovasc. Surg.*] 43, 441-452, April, 1962. 24 refs.

Of 1,000 patients who underwent open-heart surgery with total-body perfusion and extracorporeal circulation at the University of Minnesota Hospitals, Minneapolis, in 1954-60, 30 were found to have oliguria and also either a blood urea nitrogen level over 25 mg. per 100 ml. or a serum potassium level exceeding 5.5 mEq. per litre. Although there was an excess of such patients among those operated on for Fallot's tetralogy, this is a reflection only of the general severity of the operation. No specific factor was correlated with the development of renal failure. Only 4 of these 30 patients survived—a mortality of 86.7%.

[In the absence of any information on the course of the "renal failure" it is impossible to evaluate what part, if any, it played in the mortality of this group. The stated criteria of "renal failure" would be satisfied by a similar proportion of patients after partial gastrectomy.] D. A. K. Black

1081. Renal Tubular Necrosis Due to Nephrotoxicity of Organic Mercurial Diuretics

R. B. FREEMAN, J. F. MAHER, G. E. SCHREINER, and F. K. MOSTOFI. *Annals of Internal Medicine* [*Ann. intern. Med.*] 57, 34-43, July, 1962. 6 figs., 47 refs.

The authors of this paper from Georgetown University Hospital and the Armed Forces Institute of Pathology, Washington, D.C., describe 5 cases of acute renal failure due to organic mercurial diuretics, the diagnosis being confirmed at necropsy. All 5 patients had pre-existing renal damage. In the authors' view nitrogen retention is a relative contraindication to administration of mercurial diuretics. They state that the renal damage brought about by the mercurials was chiefly to the epithelium of the proximal tubule. If the condition is recognized, withdrawal of the diuretics and treatment with dimercaprol and by dialysis are indicated. The literature on organic mercurial nephrotoxicity is briefly reviewed. D. A. K. Black

Endocrinology

1082. Diagnosis and Treatment of Cushing's Syndrome

H. W. SCOTT JR., G. W. LIDDLE, A. P. HARRIS, and J. H. FOSTER. *Annals of Surgery [Ann. Surg.]* 155, 696-710, May, 1962. 5 figs., 13 refs.

This report relates the experience gained over the last 8 years in the diagnosis and management of Cushing's syndrome at Vanderbilt University Medical Center, Nashville, Tennessee, and is based on 30 patients (20 female and 10 male) aged from 9 months to 57 years. The underlying cause of the Cushing's syndrome was adrenocortical hyperplasia in 24 and adrenocortical tumour in 6. In half the cases the clinical manifestations were sufficiently obvious to make a definite diagnosis, while in the remainder the diagnosis was established by special tests. These consisted of: (1) estimation of the 24-hour urinary excretion of 17-hydroxycorticosteroids; (2) an ACTH-suppression test with dexamethasone as the agent; (3) a standard ACTH-stimulation test; and (4) in some cases blocking of 11- β -hydroxylation by "metopirone" (2-methyl-1:2-di-3'-pyridylpropan-1-one).

It was found that 17-hydroxycorticosteroid excretion was always increased above 12 mg. in adults with Cushing's syndrome. In the ACTH-suppression test, varying degrees of resistance were encountered in patients with adrenal hyperplasia, but resistance was absolute when an adrenal tumour was present; while with the ACTH-stimulation test there was excessive stimulation in patients with adrenal hyperplasia, but no effect in those with tumours. Intravenous pyelography was of value in locating the tumour in half the patients.

Surgery is regarded as the treatment of choice for tumours, while if there are florid clinical manifestations with adrenal hyperplasia, these are best relieved by bilateral total adrenalectomy. Pituitary irradiation should be reserved for mild symptoms with adrenal hyperplasia or pituitary tumours.

B. M. Ansell

1083. Zones of Cutaneous Hyperalgesia in Various Types of Goitre. (Зоны гиперальгезии кожи при различных клинических формах зоба)

I. I. NEJMARK. *Проблемы Эндокринологии и Гормонотерапии [Probl. Endokr. Gormonoter.]* 8, 69-73, May-June, 1962. 10 refs.

Few records exist of the pain syndrome which often accompanies goitre. Zakharin *et al.* studied referred pain in disease of the internal organs, and the viscerosensory reflex theory was considered to explain this. Orbell in 1934 put forward the sympathetic axon-reflex theory to explain the same phenomenon. The present author has studied in detail the zones of hyperalgesia in pyogenic processes in the lungs. Failure to trace reports of similar investigations stimulated him to study 116 patients with goitre (111 women and 5 men) from this viewpoint. He found zones of hyperalgesia in 75% of cases, varying from 62% of non-toxic nodular goitres to 84% of primary toxic diffuse goitres and 85.7% of secondary nodular diffuse goitres. The percentage was highest in severely toxic goitres of the third degree (19 out of 21) and least in non-toxic goitres (31 out of 48).

The zones occurred on the anterior and lateral surfaces of the neck, the supraclavicular areas, the shoulder girdle, and the upper third of the anterior aspect of the thorax. The area affected and the degree of sensitivity varied considerably from case to case; furthermore, successful treatment of the thyrotoxicosis reduced both the area and the sensitivity of the hyperalgesia in any given case (only in 5 patients did this not occur).
L. Firman-Edwards

1084. The Effect of Small Doses of Stable Iodine in Patients with Hyperthyroidism

R. VOLPÉ and M. W. JOHNSTON. *Annals of Internal Medicine [Ann. intern. Med.]* 56, 577-589, April, 1962. 6 figs., 36 refs.

The effect of very small doses of iodine on thyroid function was studied at the General Hospital, Toronto, in both hyperthyroid and euthyroid patients. Thyroid function was assessed at frequent intervals by clinical examination and by estimation of the serum protein-bound iodine (P.B.I.) level and the radioactive-iodine uptake by the thyroid gland. To 17 hyperthyroid patients 1 mg. of iodine, as sodium iodide, was given by mouth daily for 1 to 10 weeks. In 12 patients there was a significant reduction in the serum P.B.I. level, accompanied by comparable improvement in the clinical picture. In those patients in whom "studies were prolonged for several weeks" a gradual return to the original high level of thyroid activity was seen in spite of continued administration of iodine. Of the remaining 5 patients in this group one became much worse during treatment and 4 showed no significant response. Clinical and biochemical improvement occurred in all the 13 hyperthyroid patients given 2 mg. of iodine for 1 to 7 weeks. In 4 the serum P.B.I. level returned to normal, the improvement being sustained throughout the period of treatment and for several days thereafter. In 5 patients there was a sustained improvement in the serum P.B.I. concentration, although it did not fall completely to normal. The level in the remaining 4 patients fell initially, then rose again later during treatment but did not reach the high control level. A daily dose of 4 mg. of iodine was given to 2 hyperthyroid patients for 8 and 16 days respectively. In both there was a fall in the serum P.B.I. level to normal with an accompanying clinical improvement. Thyrotrophin, 10 units daily, was given concomitantly with iodine to one of the patients showing a response to a daily dose of 1 mg. of the latter; there was a small but significant rise in the serum P.B.I. level. No effect was observed when one of the patients who responded to 2 mg. of iodine was similarly treated. Thyrotrophin was given to 2 hyperthyroid patients for 4 days before and for 4 days after treatment with iodine (2 mg. daily) was started. The serum P.B.I. level fell and the clinical state improved after iodine was given, in spite of the simultaneous administration of thyrotrophin.

These results demonstrate the therapeutic efficacy of very small doses of stable iodine in hyperthyroidism. In the authors' view the rapidity with which the serum P.B.I. level fell in response to iodine suggests that the release of thyroid hormone from the gland must be inhibited, while the sustained effect suggests that a block in hormone synthesis is also produced. These effects would appear not to be medi-

ated through suppression of the pituitary secretion of thyrotrophin, but may possibly be due to inhibition of the action of thyrotrophin within the thyroid. Of 11 euthyroid subjects given 1 to 20 mg. of iodine daily for 3 to 36 weeks, none showed any reduction in the serum P.B.I. level. Similarly, iodine failed to inhibit the stimulating effect of thyrotrophin upon thyroid function of a euthyroid subject. There is, therefore, a difference in the action of small doses of iodine upon the thyroid glands of hyperthyroid and euthyroid subjects. However, this difference may well be only quantitative.

H.-J. B. Galbraith

1085. Evidence for Calcitonin—a New Hormone from the Parathyroid that Lowers Blood Calcium

D. H. COPP, E. C. CAMERON, B. A. CHENEY, A. G. F. DAVIDSON and K. G. HENZE. *Endocrinology* [Endocrinology] 70, 638–649, May, 1962. 7 figs., 19 refs.

In a previous study (*Nature* (Lond.), 1962, 193, 381; *Abstr. Wld Med.*, 1962, 32, 39) two of the present authors obtained experimental evidence of the presence of a new hormone from the parathyroid gland which lowers the calcium level of the blood. Further experiments on dogs providing additional evidence of the existence of this hormone are described in this paper from the University of British Columbia, Vancouver. The plasma calcium level was determined by a method of potentiometric titration with EDTA (disodium ethylenediamine tetraacetate), a semi-automatic modification of the method of Fales being used. In the assay procedure, the one-hour control period before injection of the test material was considered acceptable only if four plasma samples collected during that period agreed within ± 0.05 mg. per 100 ml. With this technique the authors found that perfusion through the thyroid and parathyroid glands of blood with a high calcium content caused a prompt fall in the systemic plasma calcium level.

Further experiments are reported which show that the effect is not due to the thyroid alone or to suppression of parathyroid hormone production. The hypocalcaemic factor is present in plasma from high-calcium perfusates but not from normal blood perfusates. It produces a maximum fall in calcium level in 20 minutes and the effect is over in one hour. Activity of the same type has been observed in commercial parathyroid extracts and in special beef parathyroid extracts which are free from parathyroid hormone activity. The name "calcitonin" is suggested, since the substance is involved in the regulation of the normal "tone" of calcium in the body fluids, being complementary in action to parathyroid hormone.

M. C. G. Israëls

1086. Corticosteroid Therapy in Surgical Emergencies. (Неотложная кортикостероидная терапия при хирургических вмешательствах)

V. E. VOLKOV. *Советская Медицина* [Sovetsk. Med.] 25, 82–86, May, 1962. 13 refs.

Acute abdominal conditions may lead to adrenocortical insufficiency, which may be increased by surgical intervention. Tests for adrenocortical insufficiency should therefore be carried out in all cases of acute abdominal emergency. Many of the usual tests take a long time to perform and operation cannot be delayed until the results are available. However, arterial hypotension which does not respond to transfusion of blood or fluid or to administration of vasoconstrictor drugs may be a sign of adrenocortical hypo-

function. In such cases 50 mg. of hydrocortisone should be given intravenously, response to which confirms the diagnosis of adrenal hypofunction. The hydrocortisone may be given with glucose or saline, and in very severe shock it can be injected into an artery. The dosage varies from 25 to 125 mg., the rate of administration depending on the degree of shock. As hydrocortisone dissolves slowly in watery solvents, it is expedient to dissolve it in alcohol and add it to a 5% solution of glucose or to physiological saline. The author has used this treatment with success in 38 patients subjected to a major operation and in 2 cases of traumatic shock. In only 3 cases was a second injection of hydrocortisone required.

L. Firman-Edwards

1087. Adrenalectomy for Hopeless Carcinoma of the Prostate

R. F. BOWERS. *Archives of Surgery* [Arch. Surg.] 84, 421–424, April, 1962. 10 refs.

Bilateral adrenalectomy was performed, at the Veterans Administration Medical Teaching Group Hospital, Memphis, Tennessee, on 16 patients with hopeless carcinoma of the prostate. The patients had previously had oestrogens and orchidectomy, after which painful or debilitating metastases appeared. One patient died from a cerebrovascular accident 2 days after the operation. Complications were otherwise not serious. Replacement therapy was not a difficult problem. Of the 15 survivors, 14 experienced remarkable relief from pain and required no narcotics until a few weeks before death. The exception had pain from local visceral spread and not from bony metastases. One paraplegic patient was able to walk with only slight assistance 3 weeks after the operation and recovered control of the sphincters. Another paraplegic patient experienced similar improvement, although more slowly and to a lesser degree. One patient had remarkable relief from a severe deformity. Survival rates after operation were, however, disappointing, the average being 9 months, the longest 2 years and 5 months.

A. Gordon Beckett

1088. Cyclic Progestational Therapy of Amenorrhoea

J. LACNY. *Canadian Medical Association Journal* [Canad. med. Ass. J.] 86, 931–933, May 19, 1962. 10 refs.

This report from the Saskatchewan Training School, Moose Jaw, Saskatchewan, concerns 9 mentally deficient women, 8 with secondary amenorrhoea and one (a girl of 17) who had never menstruated. Of the 9 patients 8 were between 18 and 26 years of age; all had marked menstrual irregularity, with an average of 3 periods a year. Six of them, in whom endogenous production of oestrogen was believed to be adequate, received 250 mg. of hydroxyprogesterone caproate in a single injection once a month for a period of 2 to 4 months. In 5 of the 6, bleeding occurred 10 to 30 days after each injection, while in the sixth, 2 of every 3 injections failed to induce bleeding. In one of the 5, regular menstruation ensued; in another, periods continued for 6 months. The remaining 3 of the 9 patients (including the girl of 17 who had never menstruated) received cyclic therapy with 5 mg. of oestradiol valerate intramuscularly followed 2 weeks later by 5 mg. of oestradiol valerate and 250 mg. of hydroxyprogesterone caproate intramuscularly. After 4 months of cyclic therapy, regularity was established in one of the 3; in another, periods occurred every 3 months for 6 months after the treatment;

the girl of 17 had light to moderate bleeding for 2 to 6 days while the treatment lasted. There were no side-effects. Behaviour was much improved in the one patient whose periods became regular after several single injections of hydroxyprogesterone caproate. The amount of bleeding induced was moderate in all the cases. *V. C. Medvei*

DIABETES MELLITUS

1089. Studies on Steroid Treatment of Chronic Insulin Resistance

J. B. FIELD. *Diabetes [Diabetes]* 11, 165-170, May-June, 1962. 3 figs., 23 refs.

The author studied insulin antagonists (or antibodies) in 5 diabetic patients who were successfully treated with corticosteroids for insulin resistance. Before treatment all 5 required more than 400 units of insulin daily; afterwards the daily requirement ranged from 50 to 125 units.

The plasma insulin-binding capacity fell considerably in 4 out of the 5 cases, but the correlation between the decreased dosage and the fall in the insulin-binding capacity was not good. There was at least a tenfold reduction in the titre of circulating insulin antagonists as measured by the radiopharm assay. The rate of disappearance of radioactive-iodine-labelled insulin remained the same in one patient after treatment with corticosteroids. In the other so investigated the rate was accelerated, and was the same whether the ^{131}I -labelled insulin was given either 48 hours or only 3 hours after the usual daily dose of 125 units of insulin.

The author suggests that the beneficial effects of corticosteroid therapy may be mediated by several different mechanisms. Insulin antagonism appears to rest in the γ -globulin and so may be considered as being due to antibodies to insulin. As judged by the fall in insulin-binding capacity, antibody production was suppressed in 4 of the 5 cases. Although the half-life of γ -globulin is about 14 days, most of the cases responded to the corticosteroids well within that time. He points out that it is not established that antibodies are the cause of insulin resistance, partly because of the lack of correlation between the decreased titre of antagonists and the change in insulin requirement effected by the corticosteroids, and partly because chronic insulin resistance has been reported in the absence of increased antibodies to insulin.

A. Gordon Beckett

1090. Pyruvate in Diabetes Mellitus: Concentrations in Urine and Blood

J. ANDERSON and V. MARKS. *Lancet [Lancet]* 1, 1159-1161, June 2, 1962. 5 figs., 9 refs.

At King's College Hospital, London, the authors studied the effect of insulin on pyruvate and α -oxoglutarate concentrations in the blood and urine of 16 diabetic subjects—6 insulin-requiring males, aged 18 to 40, whose need for insulin was absolute, and 10 obese males and females, aged 40 to 70, who did not require insulin—and 6 healthy control males aged 20 to 25. In all the diabetic subjects the disease was judged to be well controlled.

In the first test the treatment of the diabetic with insulin or oral drugs was discontinued overnight; the changes in blood concentration and urinary excretion of glucose, oxoglutarate, and pyruvate were then measured in all subjects after the administration of 100 g. of glucose. In the

second test, insulin therapy of the diabetics was not discontinued and all subjects were given 5 units of insulin intravenously with the 100 g. of glucose. Most subjects took part in both tests.

During the tests the mean α -oxoglutarate concentration in the blood was the same in the various groups and its urinary excretion did not alter significantly. During the first test blood pyruvate concentration in the fasting state was similar in all groups, but after the ingestion of glucose it rose significantly in the healthy subjects and the obese diabetics, but not in the diabetics who required insulin. When insulin was given, no such rise was observed in the healthy subjects and the obese diabetics, but, in contrast, there was a significant rise in the insulin-requiring patients. The rate of excretion of pyruvate was significantly higher in the insulin-requiring diabetics than in either the obese diabetics or the controls, and this difference persisted after insulin injection.

The results suggest that the kidneys of insulin-requiring diabetics cannot reabsorb pyruvate to the same extent as can those of obese diabetics not requiring insulin or of healthy subjects. In the insulin-requiring diabetics the urinary excretion of pyruvate was not significantly diminished when insulin was given with glucose in the second test; although the pyruvate load delivered to the kidney was more than doubled, showing that the renal pyruvate excretion improved somewhat with insulin administration. This defect is unlikely to be due to the glycosuria *per se*. The authors conclude that insulin-requiring diabetics have a defect of carbohydrate metabolism which is not controlled by insulin.

A. Gordon Beckett

1091. Small-vessel Disease of the Lower Extremity in Diabetes Mellitus. [In English]

J. PEDERSEN and S. OLSEN. *Acta medica Scandinavica [Acta med. scand.]* 171, 551-559, May, 1962. 1 fig., 12 refs.

In this paper from the Bispebjerg Hospital, Copenhagen, is described a study of the histological changes in the small blood vessels in diabetes mellitus. The material was obtained from 20 living diabetic patients—by skin and muscle biopsy from the calves of 16, from the toes of 2, and from the amputated lower limbs of 4. Biopsy specimens from 4 non-diabetic patients with ischaemic impairment of the circulation in the lower extremities served as control material. Characteristic forms of angiopathy were seen in the diabetic group. An important feature was thickening of the intima of the small arteries due to endothelial proliferation. A split-up cellular layer, with a delicate network of fibres between the individual cells, was present in the intima. These fibres gave a positive periodic-acid-Schiff (P.A.S.) reaction. In addition, P.A.S.-positive thickened basement membranes were seen in the capillary walls, and there were increased quantities of P.A.S.-positive substance in the arterioles and small arterial branches. In the control series, P.A.S.-positive thickening of the capillary basement membranes was occasionally found, but was slight in extent.

The clinical significance of these results is discussed. It is postulated that a degree of impairment of blood supply which would not cause gangrene or necrotizing ulcers in the lower limbs of non-diabetic subjects will do so when diabetes is present. This is due to peripheral angiopathy and explains why conservative management, including conservative surgery and prophylactic measures, is so important in diabetic patients.

I. McLean Baird

The Rheumatic Diseases

1092. Influence of Salicylate Administration on Iron Metabolism

G. IZAK, K. GALEWSKY-STEIN, J. MENCZEL, and J. J. GROEN. *Blood [Blood]* 19, 601-611, May, 1962. 7 figs., 9 refs.

Papers have appeared during recent years showing that the administration of salicylates may cause iron-deficiency anaemia, presumably as the result of blood loss through the gastro-intestinal tract. This report from the Hebrew University, Jerusalem, describes an investigation carried out on 11 subjects to clarify the role of salicylates in the causation of anaemia of this type. The authors tested the possibility that in addition to any effect upon the mucous membranes of the stomach and intestines, salicylates may interfere with the metabolism of ingested iron.

It was found that in every subject given salicylates in a dosage of 3 to 4 g. daily, the serum iron level fell, to rise again when salicylates were withdrawn. The possibility that this might result from interference, by the salicylate or its metabolism, with the determination of the serum iron level was ruled out; nor was it due to the removal by venipuncture of blood for testing. The amount of blood lost through the gastro-intestinal tract was measured in 3 patients and was found to be only 3 ml. per day throughout salicylate administration. It seemed, therefore, that blood loss was not the cause of the fall in the serum iron concentration. It was also shown that during administration of salicylates the survival time of erythrocytes was diminished; this, the authors consider, suggests that in these cases there may be interference with the metabolism of iron through some mechanism as yet unknown.

W. S. C. Copenan

1093. Determination of Activity of the Rheumatic Process in Children by Estimation of the Serum Sialic Acid Level. (Определение активности ревматического процесса у детей на основании лабораторного исследования сыворотки крови на сialовую кислоту)

M. B. ŠOR. *Вопросы Охраны Материнства и Детства [Vop. Okhran' Materin. Dets.]* 7, 47-48, May, 1962. 2 refs.

The author has investigated the sialic acid level in the blood serum of 109 rheumatic children; of whom 56 were in an active phase and 53 in a quiescent phase of the disease. Serum from 24 healthy children was used as control. The serum sialic acid level may be regarded as an index of the total amount of mucoproteins in the blood. The value was determined by the method of Hess: 1 ml. of blood serum was mixed with 1 ml. of 10% trichloroacetic acid; the mixture was heated in a water bath at boiling point for 5 minutes, then cooled in iced water for a further 5 minutes and centrifuged; to 0.4 ml. of the supernatant liquid was added 5 ml. of a 5% solution of concentrated hydrochloric acid in glacial acetic acid, and the mixture heated in the water bath for 30 minutes and again cooled to 0° C.; the crimson fluid was then estimated colorimetrically. In each case the erythrocyte sedimentation rate (E.S.R.) and the blood protein level were determined and Waldman's cup test, Weltmann's test, and electrocardiography were carried out.

The sialic acid titre in healthy children varies from 0.1 to 0.22 unit. In children in the active phase of rheumatism the level was high—0.221 to 0.4 unit; while in the quiescent phase it was 0.1 to 0.225 unit (average 0.17 unit). The sialic acid level was raised in 84% of children with clinically active disease, while the E.S.R. was raised in only 77%, and the results of the other tests were positive in only 30 to 33%. The author therefore regards this relatively simple test as more reliable than any other. It is, moreover, specific. In a boy of 8 admitted to hospital with a diagnosis of acute rheumatism the serum sialic acid level was only 0.04 unit, and the correct diagnosis proved to be acute osteomyelitis. In another boy of 12 in the active phase of rheumatism but without joint symptoms the E.S.R. was only 25; the serum sialic acid level, however, was 0.36 unit, which corresponded to the severity of the rheumatism as evidenced by acute carditis.

L. Firman-Edwards

1094. The Aetiology and Treatment of Primary Chronic Rheumatism. (Betrachtungen über die Ätiopathogenese und Therapie des primär chronischen Rheumatismus)

N. EFTIMESCU. *Zeitschrift für die gesamte innere Medizin und ihre Grenzgebiete [Z. ges. inn. Med.]* 17, 383-389, May 1, 1962. 2 figs., 14 refs.

The author, on the basis of the hypothesis that rheumatoid arthritis, ankylosing spondylitis, and certain other forms of arthritis may result from hypersensitivity to a staphylococcal antigen, has treated 188 patients with increasing doses of staphylococcal vaccines, at first given intradermally and later subcutaneously. In 148 of the 157 patients who completed the course the results compared favourably with those of the therapeutic methods previously used.

[In the absence of an appropriate control series, and in a disease with as variable a clinical course as rheumatoid arthritis, it is difficult to assess the significance of these findings.]

G. L. Asherson

1095. Inhibition of Negative Nitrogen Balance by an Anabolic Agent (Methandrostenolone) during Corticosteroid Therapy (Dexamethasone) in Rheumatoid Arthritis

H. RUCHELMAN and R. V. FORD. *Metabolism: Clinical and Experimental [Metabolism]* 11, 524-529, May, 1962. 4 figs., 9 refs.

A negative nitrogen balance may be observed in many forms of chronic disease and in old age. The excessive catabolism which characterizes rheumatoid arthritis may be aggravated by corticosteroid therapy. Testosterone causes an increase in nitrogen retention, but the use of this drug is limited by undesirable side-effects, notably virilization in women.

At the Veterans Administration Hospital, Houston, Texas, nitrogen balance was studied in 2 male patients with rheumatoid arthritis during simultaneous administration of dexamethasone and methandienone (methandrostenolone), an analogue of testosterone which is said to have minimal virilizing effects. The study was carried out over three 7-day periods: in the first, dexamethasone was given alone

in a dosage of 1.5 mg. daily, in the second this dosage of dexamethasone was combined with 5 mg. daily of methandienone, and in the third it was combined with 10 mg. daily of methandienone. A 7-day control period preceded each trial.

It was found that dexamethasone given alone increased the excretion of sodium, potassium, and calcium compared with control periods. When 5 mg. of methandienone was added the catabolic effects of dexamethasone were cancelled, the excretion of sodium, potassium, and calcium returning almost to the control level; there was, however, a slight decrease in excretion of nitrogen and of phosphorus. The combination of 10 mg. of methandienone with dexamethasone resulted in a significant retention of nitrogen and phosphorus. It is noted that dexamethasone promoted diuresis with increased excretion of sodium and that methandrostenolone had no consistent effect on the diuresis or natriuresis. No side-effects were observed. The authors conclude that methandienone is an effective anabolic agent in cases of rheumatoid arthritis given corticosteroid therapy.

William Hughes

1096. Some Clinical Features of Juvenile Rheumatoid Arthritis

H. WALSH. *Medical Journal of Australia* [Med. J. Aust.] 1, 507-510, April 7, 1962. 5 figs., 9 refs.

The records of 50 cases of juvenile rheumatoid arthritis treated between 1953 and 1960 at the Royal Alexandra Hospital for Children, Sydney, were reviewed, chiefly from the standpoint of initial symptoms. There were 30 girls, and 30 of the 50 children were under 5 years of age at the onset. The disease tended to be more severe in the younger children. Of the 43 patients who presented with joint symptoms, 9 had monarticular arthritis, usually of the knee, and this often led to an initial erroneous diagnosis of tuberculous arthritis [a mistake too often made, either because a tuberculin test is not performed or a negative result is ignored]. Of the remaining 7 patients, 4 presented with undiagnosed fever, one with a rash, one with recurrent lymphadenopathy, and one with recurrent pneumonitis and a rash. Eventually polyarthritis occurred in all 50 cases; rash, lymphadenopathy, and splenomegaly were noted in 18, 16, and 8 patients respectively. There were 4 cases of pericarditis and 2 patients had iridocyclitis, one of whom became blind. Prolonged periodic fever occurred in 31 cases, leading to much general deterioration. Anaemia and leucocytosis were common. The response to the Rose-Waaler test was invariably negative.

John Lorber

1097. A Family Study of Rheumatoid (Ankylosing) Spondylitis

I. KARTEN, D. DITATA, C. MCEWEN, and M. TANNER. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 131-143, April, 1962. 6 figs., 47 refs.

Examination of 142 close relatives of 58 consecutive patients with ankylosing spondylitis seen at the Bellevue and Manhattan Veterans Administration Hospitals, New York, revealed 6 secondary cases of the disease in 3 families, a significantly higher incidence than has been reported for the general population. The incidence of rheumatoid arthritis (3 secondary cases in 2 families) among the relatives of the patients with spondylitis was similar to the reported incidence in relatives of controls without rheumatoid disease.

Tests for rheumatoid factor gave positive results in similar proportions of the patients with spondylitis (3.3%), their asymptomatic relatives (5%), and non-rheumatoid controls (5%).

A family is described of which 5 members had ankylosing spondylitis and one had rheumatoid arthritis. Nevertheless, the authors consider that these findings do not support the view that there is a genetic relationship between the two diseases.

M. Wilkinson

1098. The Significance of Calcium Phosphate Crystals in the Synovial Fluid of Arthritic Patients: the "Pseudogout Syndrome". I. Clinical Aspects

D. J. MCCARTY JR., N. N. KOHN, and J. S. FAIRES. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 711-737, May, 1962. 11 figs., 34 refs.

The development of a rapid, simple technique for the identification of urate crystals in gouty synovial fluid led to the discovery that in certain patients with a non-typical syndrome, crystals of calcium phosphate were consistently present. Joint fluid containing these crystals, when introduced into the synovial cavities of animals and a healthy man, gave rise to an acute synovitis similar to the recurrent attacks experienced by the original patients. This syndrome, which resembles classic gouty arthritis, is, however, not associated with a raised serum urate level, and the authors consider it to be a form of "crystal-induced synovitis" which they refer to as "pseudo-gout". The condition is believed to be identical with that described in the literature under the term "chondrocalcinosis", since in the later stages it appeared that calcification of the articular cartilage might be a characteristic feature.

In the present paper from Hahnemann Medical College and Hospital, Philadelphia, the clinical features in 7 cases are described. The predominant joint involved in all the patients (5 male and 2 female over 50 years of age) was the knee, although the wrists and other joints had been involved previously in some of the cases. In 5 patients who had acute episodes the precipitating factors included trauma, surgery, and mercurial injections. The remaining 2 patients had had chronic arthritis for a considerable time with occasional exacerbations. Radiological examination revealed abnormal calcification in all cases, but the authors consider that "the identification of calcium phosphate crystals in the synovial fluid is probably a more accurate way to define this disease entity".

W. S. C. Copeman

1099. The Significance of Calcium Phosphate Crystals in the Synovial Fluid of Arthritic Patients: the "Pseudogout Syndrome". II. Identification of Crystals

N. N. KOHN, R. E. HUGHES, D. J. MCCARTY JR., and J. S. FAIRES. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 738-745, May, 1962. 3 figs., 18 refs.

In this second paper (see Abstract 1098) the authors describe the methods employed in determining the composition of the crystalline material obtained from the synovial fluid of the 7 patients. Physical and chemical studies of the crystals led to the conclusion that they are a form of calcium pyrophosphate. In the identification the use of x-ray diffraction in obtaining powder pattern photographs proved to be especially helpful, and this method and its application to similar problems are fully discussed.

W. S. C. Copeman

Neurology and Neurosurgery

1100. Electroencephalographic Study of Acute Head Injury in Children

D. SILVERMAN. *Neurology* [*Neurology* (Minneapolis)] 12, 273-281, April, 1962. 8 figs., 10 refs.

This paper from the University of Pennsylvania reports the findings in 100 children under 16 years of age in whom electroencephalography (EEG) was performed within 4 weeks of head injury. The severity of the injury was graded as "negligible" (no initial loss of consciousness but perhaps a transient dazed state), "mild" (initial loss of consciousness lasting up to one hour), "moderate" (loss of consciousness lasting from one to 24 hours and/or transient neurological abnormalities), or "severe" (loss of consciousness lasting more than one day and neurological abnormalities of long duration).

In 31 of the children the injury was regarded as negligible, in 28 as mild, in 29 as moderate, and in 12 as severe. The EEG findings were abnormal in 29% of the children with negligible injury, in 68% of those with mild injury, in 90% of those with moderate injury, and in 100% of those with severe injury. The most frequent single abnormality was delta or theta slowing in the parieto-occipital areas, and the younger the child the lower was the frequency of the slowing. The presence of fracture had little influence on the EEG findings. Follow-up examination of 56 of the patients showed that in 36 the EEG eventually became normal. The rate of recovery was unpredictable and seemed to be unrelated to the severity of the injury. Spike-and-wave patterns did not develop in any of the children, but at the time of writing only 8 had been followed up for more than a year. The author comments that posterior slowing is not a specific change, but occurs with a number of different pathological processes.

[This is a slightly disappointing paper. Closer liaison with the clinicians could have made it much more valuable.]

N. S. Alcock

1101. Diagnostic Electromyography: Clinical and Pathological Correlation in Neuromuscular Disorders

J. G. HUMPHREY and G. M. SHY. *Archives of Neurology* [*Arch. Neurol.* (Chic.)] 6, 339-352; May, 1962. 15 figs., 17 refs.

At the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland, the findings on electromyography (EMG) in 159 patients with neuromuscular disease were analysed and correlated with the findings on biopsy examination of an involved muscle and with the clinical picture.

The various parameters of muscle function observed and measured included the following: interference pattern, mean duration of the action potentials, action potential amplitude, spontaneous activity at rest and after insertion of the electrode, synchronization, conduction times, and the presence of polyphasic potentials. The EMG findings were in agreement with the pathological changes observed in muscle biopsy specimens in 135 (85%) of the cases. In 18 cases the findings were conflicting, and in a further 6 cases

the EMG was in error or inconclusive in the presence of undoubted clinical and pathological evidence of disease. The EMG findings in anterior horn cell disease, polyneuropathy, myopathy, polymyositis, sarcoidosis, and myasthenia gravis are tabulated and described in detail.

H. S. Schutta

1102. Huntington's Chorea in the Moray Firth Area

R. L. LYON. *British Medical Journal* [*Brit. med. J.*] 1, 1301-1306, May 12, 1962. 1 fig., 10 refs.

Huntington's chorea is common among fishing communities in the Moray Firth area of north-eastern Scotland. There is little marrying outside the villages and marriages tend to be with members of other fisher families. The author, writing from the Royal Northern Infirmary, Inverness, reports an investigation of 7 such families. The pedigrees are illustrated and brief histories of individual cases are given. One mother made her 6 children promise not to marry; all except one son obeyed, and his children are so far unaffected. The average age of onset was 51, which is higher than the usual stated figure. The earliest and the latest ages at which the disease showed itself were 27 and 75 years respectively. The average survival time after diagnosis was 7 years. Early evidence of mental impairment included irritability, moodiness, and neglect of home and person.

G. S. Crockett

1103. Non-hereditary Chronic Adult Chorea as a Clinical Entity

R. L. LYON. *British Medical Journal* [*Brit. med. J.*] 1, 1306-1308, May 12, 1962. 2 refs.

During a survey of families with Huntington's chorea in the Moray Firth area (see Abstract 1102) 2 patients were found with a condition resembling Huntington's chorea but in whose ancestry, which was scrutinized for the previous 100 years, no case of the disease could be traced. "No association with fisher families was known. The eldest child of one of the patients is only 37, so that it is too early yet to decide whether this patient has a hereditary condition. One speculative explanation of these cases is that they are due to spontaneous mutation."

G. S. Crockett

1104. Drug Treatment of Huntington's Chorea: a Trial with Thiopropazate

R. L. LYON. *British Medical Journal* [*Brit. med. J.*] 1, 1308-1310, May 12, 1962. 11 refs.

The author describes the results of administration of thiopropazate dihydrochloride ("dartalan"), a phenothiazine derivative, in a dosage of 10 mg. 3 times a day after meals, to 5 cases of Huntington's chorea among the fisher families described above (see Abstract 1102) and one case of non-hereditary chronic adult chorea (see Abstract 1103). The drug was given in courses of 3 months alternating with 3-month courses of inert tablets. While receiving the drug the patients were calmer and their chorea was less marked. One fisherman was able to resume mending nets. Aggressiveness was diminished, but dementia was unaffected. In some

cases the treatment appeared to have postponed or even eliminated the need for institutional treatment.

G. S. Crockett

1105. Huntington's Chorea in the Chinese

K. SINGER. *British Medical Journal* [Brit. med. J.] 1, 1311-1312, May 12, 1962. 1 fig., 5 refs.

A Chinese family of 24 members in which Huntington's chorea occurred through 4 generations is described from Castle Park Hospital, Hong Kong. The disease affected 6 members (and probably also a 7th). The age at onset ranged from 10 years to middle age. The 2 cases described in detail had chorea and dementia of varying severity. All the other affected members also had chorea and dementia except one, whose intellectual functions were preserved to the end. The 4 choreic parents in the family had between them 17 siblings, of whom 6 were affected. Of the remaining 11, 3 had died in childhood and 8 (including 2 below the age of 10 years) were well. The disease does not appear to have been described before in the Chinese.

G. S. Crockett

1106. Trigeminal Neuralgia: Its Treatment with a New Anticonvulsant Drug (G-32883)

S. BLOM. *Lancet* [Lancet] 1, 839-840, April 21, 1962. 5 refs.

Since 1940 a number of reports have appeared claiming that large doses of diphenylhydantoin sodium have a beneficial effect on trigeminal neuralgia. Others have been less enthusiastic. The present author, at University Hospital, Uppsala, Sweden, investigated the effect of the new anticonvulsant drug, G-32883 (5-carbamyl-dibenz(b,f)-azepin), which is related to imipramine ("tofranil"). He treated 22 cases of trigeminal neuralgia with diphenylhydantoin and 11 cases with G-32883. Of the former, 8 patients have remained free from pain and "9 have been helped a good deal". A slight effect only was noted by one patient, and the treatment was ineffective in 4. In 14 cases moderate to severe vertigo was noted, and in 2 this was intolerable. In 2 other patients the initial effect was "very good", but after 2 years the drug failed. These last 4 cases were helped by G-32883. Of the 11 patients treated with the latter drug, 6 became completely free from symptoms within 24 hours and 4 were left with slight feelings of numbness in the affected area; one patient was only partially relieved. Six patients complained of slight giddiness, which subsided after a few days, and in one case an exanthem appeared after a week. The patients were observed for little more than 6 months.

[No conclusions can be drawn from this report, since the period of observation of the cases is too short, no controls were used, and cases of trigeminal neuralgia are notoriously subject to spontaneous disappearance of pain sometimes as a result of suggestion. The trial should have been carried out by the double-blind technique with placebos.]

R. Wyburn-Mason

1107. Spinal Arachnoiditis

G. LOMBARDI, A. PASSERINI, and F. MIGLIAVACCA. *British Journal of Radiology* [Brit. J. Radiol.] 35, 314-320, May, 1962. 6 figs., 13 refs.

This is a report, from the Institute of Neurology, Milan, of a radiological study of 41 cases of spinal arachnoiditis, 31 of which were operated on. Myelography with iodized

oil gave the correct diagnosis in 24 (58%) of the cases. The incidence was found to be greatest in the 3rd, 4th, and 5th decades of life, the average age at the time of diagnosis being 36 years and the extremes ranging from 10 to 60 years. The cause was not always clear and sometimes only presumptive. Of 8 patients who had had cerebrospinal meningitis, the arachnoiditis had appeared after an average lapse of 14 years in 6 and after only a few months in 2. In 3 patients the arachnoiditis was preceded by trauma, without fracture, at the site of the lesion, and the disturbances began respectively some weeks, 7 months, and one year later. In another 3 patients the arachnoiditis appeared after subarachnoid haemorrhage, at intervals of 2 weeks, 3 months, and 11 years respectively, while in yet another 3 it appeared 4 months, 11 years, and 12 years respectively after intrathecal injections of antitetanus serum. One other case occurred a few months after cure of tuberculous meningitis. The aetiological factors in these 18 cases were convincing, but in the other 23 cases the histories gave little guidance. There were no cases following spinal anaesthesia.

The clinical picture is complex because of overlapping of root and cord affections; it is polymorphous and irregular in evolution and is easily confused with that of other spinal disease. Arachnoiditis has a preference for the dorsal segments of the spine, and this was the case in 28 (68%) of the patients. The lumbar portion was affected in 7 cases and the cervical in 6. The duration of clinical symptoms from onset to diagnosis ranged from 15 days to 32 years.

The myelographic findings are discussed in some detail. Complete spinal block was present in 27 cases (66%). In contrast to other affections of the spinal cord, in which the myelographic appearances are characteristic, the picture in arachnoiditis is often, like the distribution of the adhesions, bizarre and polymorphous. [The illustrations and accompanying text should be seen.]

The results of operation in 31 patients are described; these cannot be considered as outstanding. Medical treatment with antibiotics and intrathecal injection of cortisone also gave very poor results.

J. MacD. Holmes

BRAIN AND MENINGES

1108. Systemic Manifestations of Neurogenic Tumors

M. D. KOGUT and S. A. KAPLAN. *Journal of Pediatrics* [J. Pediat.] 60, 694-704, May, 1962. 2 figs., 43 refs.

The authors review 27 reported cases of neurogenic tumours in children aged 7 weeks to 14 years and describe in detail the clinical features in a case of neuroblastoma and one of ganglioneuroma seen at the Children's Hospital, Los Angeles, the patients being respectively 15 and 17 months old.

The diagnoses in the reported cases were neuroblastoma in 13 cases, ganglioneuroblastoma in 7, ganglioneuroma in 6, and a tumour characteristic "both of pheochromocytoma and ganglioblastoma" in one case. In these 29 cases of malignant tumours the characteristic findings were hypertension, diarrhoea, excessive flushing and sweating, pallor, skin rashes, and polydipsia and polyuria. There was an increased urinary excretion of catechol amines or their breakdown product, vanillylmandelic acid, in all 18 cases in which this value was determined.

A. G. Freeman

1109. **Ospolot in the Treatment of Epilepsy.** (Erfahrungen mit Ospolot in der Epilepsiebehandlung) F. RABE, H. PENIN, and A. MATTHES. *Deutsche medizinische Wochenschrift* [Dtsch. med. Wschr.] 87, 953-599. May 4, 1962. 13 refs.

The authors of this paper from the University of Heidelberg report their 2-year experience with "ospolot" (tetrahydro-2-*p*-sulphamoylphenyl-1:2-thiazine 1:1-dioxide) in the treatment of epilepsy. Of 213 patients originally given the drug, 30 had to be withdrawn from the trial because of side-effects. The remaining 183 included cases of psychomotor epilepsy (57), psychomotor epilepsy with grand mal (89), grand mal alone (8), petit mal and grand mal combined (13), and smaller numbers with Jacksonian attacks, pure petit mal, and other epileptic phenomena. In all these groups the results were disappointing compared with those obtained with the standard anticonvulsant drugs, and side-effects occurred in approximately 75% of the patients (paraesthesiae, 38%; tachypnoea and hyperpnoea, 30%; vegetative disturbances, 21%; and psychological disturbances, 14%).

The authors do not recommend ospolot for the routine treatment of psychomotor epilepsy, minor epilepsies, or grand mal, nor do they find that its association with the established anticonvulsant agents allows these to be used in lower dosage. In some cases of psychomotor epilepsy resistant to other anticonvulsants, 1 or 2 tablets of ospolot a day (higher doses usually produce side-effects) may reduce or abolish the attacks. In patients with mental retardation, lack of drive, and emotional lability, ospolot in similar low dosage may occasionally have a beneficial effect. Finally, because of its more rapid action, ospolot may be useful in controlling psychomotor epilepsy in the initial stages of treatment before the standard anticonvulsants have had time to act.

J. B. Stanton

1110. **Post-traumatic Epilepsy. Considerations in a Series of 216 Cases.** (Épilepsie post-traumatique. Considérations sur une série de 216 observations) J. E. PAILLAS, B. COURSON, R. NAQUET, and N. PAILLAS. *Semaine des hôpitaux de Paris* [Sém. Hôp. Paris] 38, 1191-1199, April 8, 1962. 3 figs., 27 refs.

The authors' summary may be translated as follows. The study [at the Hôpital de la Timone, Marseilles] of 50 cases of epilepsy following a cranio-cerebral wound and of 166 cases following a closed head injury leads to the following conclusions. (1) The incidence of epilepsy may reach 37% after open injury and 9.4% after closed injury. It is more frequent in the male and alcoholism plays an aggravating role. (2) The delay in appearance is variable: one year in 48% of cases of open injury and in 41.5% of closed injury. Epilepsy may still appear in subsequent years, even 30 years after injury in the longest instance. A convulsion occurring in the immediate post-traumatic period is not of bad prognostic significance. (3) The average delay in the appearance of epilepsy in relation to the age of the subject was 15 years in those under 3 years of age and one year in those older than 15 years. (4) The delay in onset is also related to the site of the trauma, being short in Rolandic-parietal lesions (6 months to one year), long in frontal lesions (6 to 7 years), and very prolonged in occipital lesions (13 years). The average time for appearance in temporal lesions was from 2½ and 3½ years. (5) The damage to the cerebral parenchyma, especially the cortex, plays a more important

part in determining the period of "incubation" than the severity and duration of the initial coma. (6) The attacks are most often generalized: 32.5% after open wounds and 45% after closed injury. Psychomotor attacks are almost as frequent: 31.5% after open injury and 36% in closed injury. Jacksonian fits come third in order of frequency, other types being exceptional. (7) Post-traumatic epileptics often show psychiatric symptoms, so much so that the appearance of epilepsy is the more to be feared in patients with psychiatric sequelae. Pneumographic abnormalities may be present in these cases. (8) Electroencephalographic (EEG) tracings show focal unilateral abnormalities in 78% of cases after open injury and in 62% after closed injury. Diffuse abnormalities are found in 5% and 19% of cases respectively. Tracings are normal in 10%. The most frequent focal localization is in the temporal region. The prediction of epilepsy by the EEG following cranial injury is very difficult, but the repetition of tracings at regular intervals may give useful prognostic information. (9) Intensive medical treatment brings about clinical cure in 50% of cases and neurosurgery may also produce a 50% cure rate in cases suitable for operation.

J. MacD. Holmes

1111. **The Effects of Adrenaline, Noradrenaline, and Isoprenaline on Parkinsonian Tremor**

C. CONSTAS. *Journal of Neurology, Neurosurgery and Psychiatry* [J. Neurol. Neurosurg. Psychiat.] 25, 116-121, May, 1962. 11 figs., 17 refs.

The aggravation of tremor which normally occurs when a patient with Parkinsonism is emotionally disturbed has been attributed to the release of adrenaline. In view of the divergence of opinion as to the exact site of action of adrenaline on the central nervous system, the author, at the Institute of Neurology, London, studied 25 patients to ascertain the site at which catechol amines act in increasing Parkinsonian tremor. The apparatus used for recording tremor was that previously described by Marshall and Walsh (*J. Neurol. Neurosurg. Psychiat.*, 1956, 19, 260).

The intramuscular injection of 1 ml. of a 1 in 1,000 solution of adrenaline produced a marked increase in the amplitude of tremor in 24 of the 25 patients; in 8 patients the frequency of the tremor was also increased. A previous injection of normal saline in 10 patients had produced no change in the amplitude or frequency of the tremor, thus excluding the possibility that emotional factors alone were responsible for these findings. Oral inhalation of 0.3 ml. of "neopine" containing 1% of isoprenaline sulphate produced an effect similar to, though less marked than, that of adrenaline in 3 of 5 patients studied. No significant change in the amplitude or frequency of tremor occurred after intravenous infusion of noradrenaline.

Experiments were also devised to ascertain the site of action of adrenaline on the central nervous system. These consisted in comparing the effects on the tremor of intra-arterial and intramuscular injection of adrenaline, and of intramuscular injection of adrenaline after administration of ganglion-blocking drugs, and of drugs acting on post-ganglionic sympathetic nerve fibres and effector cells. These experiments showed no evidence of a peripheral action of adrenaline; a central action is therefore postulated, its most probable site being the reticular formation of the brainstem.

A. G. Freeman

Psychiatry

1112. Cholinesterase-like Substance in the Parotid Saliva of Normal and Psychiatric Patients

D. B. GIDDON and V. F. LISANTI. *Lancet [Lancet]* 1, 725-726, April 7, 1962. 11 refs.

Parotid saliva contains a cholinesterase-like substance which may be assayed by a sensitive modification of a method for estimation of serum pseudocholinesterase, β -carbonaphthoxicholine iodide being used as substrate. The salivary enzyme is not inhibited by physostigmine and its concentration in saliva is about 10^{-3} that of the serum. The present paper reports a preliminary study of the concentration of this substance in saliva obtained from normal subjects and from a group of psychiatric patients.

The 29 psychiatric patients (mean age 24 years) had all been recently admitted to hospital and most were classified as acute or affective schizophrenics. The normal group numbered 49 and were of a similar age. [No further data concerning the subjects are given.] Parotid saliva (8 to 10 ml.) was collected from Stensen's duct by means of a Curby parotid cap (*J. Lab. clin. Med.*, 1953, 41, 493). Flow was stimulated with chewing gum. The mean concentration (units per 100 ml., followed by the standard deviation) of the salivary cholinesterase-like substance in the patients was 0.021 ± 0.022 (range: zero to 0.08) and in the normal control subjects 0.036 ± 0.014 (range: 0.013 to 0.086). The mean salivary flow rates (ml. per min.) were 0.24 ± 0.16 (range: 0.03 to 1.00) in the patients and 0.77 ± 0.33 (range: 0.36 to 1.78) in the controls. For both measures the differences between the groups were significant ($P=0.01$). The results for the psychiatric patients tended to fall into two groups: in some there was little or no measurable activity of the salivary enzyme, while in others the values were nearer those of the normal group. The variance of results was significantly greater in the patients. No correlation between enzyme concentrations, flow rates, Funkenstein test measures, physical characteristics, or diagnostic categories could be discerned for the whole group of patients. In 16 recently admitted patients who had received no treatment, enzyme concentrations were directly proportional to flow rates and indirectly to the Funkenstein measures of circulating adrenaline-like substance. In additional experiments on a normal group the concentration of salivary enzyme was found to be reduced by the expectation of stress, but no correlation with flow rate was observed. [Data are not given for these experiments.] The authors consider that the level of the salivary enzyme and the salivary flow rate may together provide a useful measure of autonomic balance.

R. Rodnight

1113. Neurosis in Hospital and General Practice

N. KESSEL and M. SHEPHERD. *Journal of Mental Science [J. ment. Sci.]* 108, 159-166, March [received May], 1962. 2 figs., 42 refs.

The authors compare some aspects of the incidence of neurosis in Great Britain as indicated by mental hospital in-patient and out-patient records and by a review of 28 studies on psychiatric morbidity in general practice.

According to the Registrar-General's Mental Health Reports admission rates for neurosis rose steadily during the

1950's. In 1953 the rates per 100,000 adults were for males 29 and for females 34; in 1956 the corresponding figures were 32 and 44. Since the total figures of those treated as out-patients do not allow of diagnostic analysis, the authors "sampled" the figures for the county of Buckinghamshire for 1959. These give rates of 73 per 100,000 for males and 123 for females. Further comparison of the Buckinghamshire figures with the triennial reports from the Maudsley Hospital, London, leads to the conclusion that, during the late 1950's, between 60,000 and 70,000 new cases of neurosis were seen annually at psychiatric out-patient clinics.

Studies of the incidence in general practice gave, as might be expected, widely ranging results, from 5% to 30% of persons registered. As the authors point out, there are many reasons for these differences, one being nosological and another the orientation of different practitioners towards psychiatric illness. Practitioners with an "organic" viewpoint rarely give an incidence above 10%, but figures of 40% or more have been cited by those with an inclination towards psychoanalysis. It is clearly not possible to draw firm conclusions from such data. All studies confirm a higher incidence of neurosis among women, but no such consistency can be observed in age-specific rates. Hospital figures, both in-patient and out-patient, show a peak in relatively early life falling slowly with age, whereas figures in general practice show no such decline, and suggest that the incidence remains constant in middle life and may even rise in old age. To explain these inconsistencies, and for our better knowledge generally, there is need for closer liaison between general practitioners and psychiatrists.

Rex Matthews

1114. Neurotic Crises in Students: Problems of Psychotherapy and Orientation. (Les conditions de la crise névrotique chez les étudiants et les problèmes de psychothérapie et d'orientation)

R. CANESTRARI. *Annales médico-psychologiques [Ann. méd.-psychol.]* 120, 874-884, May, 1962.

Experience of a psychiatric service for students at the University of Bologna is reported and compared with that of a similar service at the University of Salerno.

University life is essentially a period of stress, because it is a period of transition between school and professional activity. The student's chief difficulty is that he is still an adolescent and has therefore still to resolve the problems of his personal identity and of his sexual and social roles. There is, moreover, a contradiction between the traditional student life, bohemian and romantic, and the modern need, often economically determined, for concentrated study. Poor adaptation to university life can be recognized by scholastic failure, and lack of self-confidence may give rise to sexual and social problems. Financial difficulties may produce feelings of guilt towards the family and lead to isolation, which is increased by the social distance between teacher and student, by the social and psychological structure of student life, and by the need to study for examinations. The resulting conflict may cause disorientation of the ego, with loss of efficiency at work and social maladjustment. Such a crisis is especially liable to occur in the presence of

neurotic predisposition or of special personal problems. The latter may result from upbringing in an atmosphere of indulgence or of compensated hostility and are prejudicial to the long-term stability required to study for an examination which will take place in the distant future. When financial difficulties are severe, success in the examination, which may even confer exemption from fees, becomes vital. In these circumstances university life is an economic operation leading to complete isolation. The student may do remunerative work in addition to study and may live far from the university, thus being prevented from joining in other university activities.

In southern Italy, as, for example, at Salerno, university life is a means of entry into a higher social class or to the acquisition of social prestige, and thus brings about further conflict and isolation from the original social group. Many students complained of sexual difficulties, which were often related to poor application to their work. Migraine, asthenia, somnolence, "blocking" in examinations, and psychosomatic symptoms such as gastritis, colitis, and tachycardia were common defence mechanisms. Others included perfectionism, fugues, and systematic fantasies. Students who developed major psychoses were generally admitted to hospital, but cases of depression were usually treated on an out-patient basis. Psycho-analysis was not readily available and treatment consisted, in addition to the administration of tranquilizers, of discussion, based on the methods of Carl Rogers, of present situations, of the acceptance of responsibility, of unpleasant reality, and of personal difficulties.

The experiment has been rewarded with considerable success and a report with detailed results is in preparation. The author considers that a service of this type is essential in a university.

J. S. Bearcroft

4115. Prognostic Factors in Treatment of Depressive States with Imipramine

L. G. KILOH, J. R. B. BALL, and R. F. GARSIDE. *British Medical Journal [Brit. med. J.]* 1, 1225-1227, May 5, 1962. 7 refs.

Whether or not depressive states form a homogeneous continuum, differences certainly exist in their response to treatment. These differences were studied in 97 patients at the Royal Victoria Infirmary, Newcastle upon Tyne, who were given imipramine for depressive states. Each patient was assessed on 60 items; 36 of these, including personality traits, previous history, and symptoms of present illness, were subjected to a discriminant function analysis with respect to outcome of treatment, "good" or "poor", at 6 months. The results indicated that patients with depressive states are more likely to respond to imipramine if they are 40 or more years old; if the onset of the illness is insidious and the duration is less than a year; and if the depression is qualitatively different from "normal" depression and is associated with early waking and a weight loss of 7 lb. (3.2 kg.) or more. Patients who respond poorly are younger; their illness more often starts suddenly in relation to external factors; they tend to be irritable, self-pitying, and unable to concentrate; their sleep is restless; and they may show hysterical or hypochondriacal features. The clinical picture in those responding to imipramine is characteristic of endogenous depression, while that in patients who fail to respond is more characteristic of neurotic depression.

The authors consider that their findings not only provide a basis for predicting individual response to treatment, but also lend support to the view that endogenous and neurotic depression are separate entities. The 97 patients were subdivided into endogenous or neurotic groups according to defined criteria and independently of response to treatment. In those cases in which the diagnosis was reasonably certain, a highly significant relationship was found between outcome and type of depression. Of 15 patients with endogenous depression 14 improved and remained well after 6 months' treatment, a result achieved by only 11 of the 32 patients with neurotic depression.

It is concluded that treatment with imipramine is indicated principally in those cases showing features associated with the diagnosis of endogenous depression. A far less satisfactory response is obtained in cases in which the features suggest a neurotic depression.

Alan A. Black

1116. Proposal of a Psychopharmacological Test ("Stimulation Threshold") for Differentiating Neurotic from Psychotic Depressions: Preliminary Report. [In English]

F. GIBERTI and R. ROSSI. *Psychopharmacologia [Psychopharmacologia (Berl.)]* 3, 128-131, 1962. 4 refs.

The work of Shagass suggested that the "sedation threshold" to amylobarbitone sodium, as measured by the onset of slurred speech and electroencephalographic changes, is significantly lower in psychotic than in neurotic depression. Other studies have cast doubt on this hypothesis. The present paper from the University of Genoa describes an investigation of the action of amphetamine in 15 patients with psychotic depression and 15 with neurotic depression. A dose of 30 mg. of methylamphetamine hydrochloride was given intravenously at a rate of 1 mg. every 30 seconds. Pulse rate, blood pressure, and other physiological and behavioural changes were noted during the injection. Each patient also received an injection of a placebo. A "stimulation threshold" was defined on the basis of physiological and psychological changes and it was found that this level was reached with significantly less amphetamine in the cases of neurotic depression than in those of psychotic depression. The correlation with anxiety and the response to drugs and electric convulsion therapy are discussed. These preliminary results, which appear to agree with those of Shagass, justify further research.

B. M. Davies

1117. Fingerprints in Schizophrenia

T. RAPHAEL and L. G. RAPHAEL. *Journal of the American Medical Association [J. Amer. med. Ass.]* 180, 215-219, April 21, 1962. 5 figs., 13 refs.

Because finger patterns are constitutional in nature, previous workers have tried to ascertain if the patterns of schizophrenic patients have any special characteristics. In view of the inconclusive results, a further study was carried out at the Ypsilanti State Hospital, Michigan, on 100 male patients, selected by strict diagnostic criteria and free from other conditions known to influence finger patterns. Prints, available because legally required in all Michigan State hospitals, were classified and checked by police experts; pattern distributions were then compared with the largest and most reliable general population series available, that compiled by Scotland Yard.

Although the general pattern characteristics and distributions of the two series were similar, thus affording some

validity to the comparison, differences existed in the relative frequency of certain types: in the schizophrenic group there was a greater incidence of whorls and arches and fewer loops. [These differences are not evaluated statistically.] One further anomaly was noted: ridge dissociation, due to interference of ridge differentiation in foetal life, was seen in 18 patients. This compares with completely negative findings among 4,000 controls used in the original study describing this condition, making the present finding very highly significant ($P > 0.0001$).

Such abnormality has been found in 5 other congenital conditions and, together with the earlier findings, reinforces the concept of a primary general genotypic deficit, of which finger patterns may be a manifestation, rendering the host vulnerable to a wide range of disorders. The authors urge the value of dermatoglyphic study as a genetic lead not only in schizophrenia, but for medicine in general.

Alan A. Black

1118. Some Observations on the Concept of "Reactive" and "Process" Type Schizophrenia

R. G. WALKER. *Journal of Clinical and Experimental Psychopathology and Quarterly Review of Psychiatry and Neurology* [J. clin. exp. Psychopath.] 23, 7-10, Jan.-March [received May], 1962. 5 refs.

The concept that there are two types of schizophrenia—the "reactive" type of acute onset, often apparently related to environmental factors causing stress, and a "process" type which is insidious in onset and not obviously related to psychosocial stress—was examined in patients at the Veterans Administration Hospital, Brockton, Massachusetts. For this purpose the frequency of relapses in 90 schizophrenic patients who had been discharged from hospital in remission was studied. In 70 patients there were remission and discharge within one year of admission to hospital and this group were regarded as having the reactive type of schizophrenia. In 20 patients the discharge in remission followed a hospital stay of one year or longer, during which schizophrenic symptoms had continued to be apparent; these were considered to be suffering from the process type. After a follow-up period of 2 years from the time of discharge from hospital, no difference in relapse rate was observed between the two groups. The author considers that there is no justification for the use of the terms "reactive" and "process" schizophrenia with the implication of differing aetiology.

J. B. Stanton

1119. Psychiatric Appraisals of Parents and Siblings of Schizophrenic Children

D. MEYERS and W. GOLDFARB. *American Journal of Psychiatry* [Amer. J. Psychiat.] 118, 902-908, April, 1962.

This is a preliminary report of a psychiatric study, still in progress at the Henry Ittleson Center for Child Research, New York, of parents and siblings of 45 schizophrenic children. The children were aged from 6 to 11 years and had shown symptoms before the age of 5 years; all came from unbroken homes. The diagnosis of "childhood schizophrenia" was made by 3 psychiatrists independently. The children were divided by a neurologist into (a) those with a history or signs of neurological impairment ("organic"), and (b) those without ("non-organic"). The ratio of males to females in the organic group was 3.8 to 1, and in the non-organic group 1.7 to 1. The organic group contained a relatively high number of firstborn children.

The parents and siblings were investigated by 4 psychiatrists who had had training at a psychoanalytic clinic. Among the parents regarded as schizophrenic were borderline, pseudoneurotic, latent, ambulatory, and compensated cases—that is, schizoid personalities. Schizophrenia was present in 21% of the mothers of children in the organic group and in 44% of the mothers of those in the non-organic group. The over-all incidence of maternal schizophrenia was 29% and of paternal schizophrenia 13%.

The psychological adequacy of the home was appraised by a 3-hour visit with all the family present. Only families without parental schizophrenia were in the highest range of family adequacy, rating 140 to 280, those with parental schizophrenia rating 100 to 200. (The highest family adequacy rating was 294.)

The authors are aware that there may be varying combinations of aetiological factors, including somatic (acquired and/or genetic) and psychological factors, at work in a single child. They draw attention to the different features of the organic and non-organic types of disease.

G. de M. Rudolf

1120. Indole Metabolites in Schizophrenic Patients: Urinary Excretion

G. G. BRUNE and H. E. HIMWICH. *Archives of General Psychiatry* [Arch. gen. Psychiat.] 6, 324-328, April, 1962.

This paper, from the Galesburg State Research Hospital, Illinois, reports a longitudinal study of the urinary content of tryptamine and total indole-3-acetic acid in relation to reserpine medication and to different degrees of psychotic activity in 20 male schizophrenic patients. The patients selected were in good health, and were given a constant protein diet of 100 g. of protein a day for one week before and then throughout the investigation, the protein intake being recorded. Urine was collected for successive 24-hour periods and assayed for tryptamine by a specific fluorimetric technique and for indole-acetic acid by a photometric method. The activity of the psychosis was rated in each patient in 5 different degrees of severity [briefly outlined], assessed according to clinical impression. [Individual cases are not described.] A total of 835 24-hour specimens of urine were analysed. These had been collected during successive periods of [apparently] one week, from patients receiving, in the following order, placebo 1, reserpine 1 (4 mg. per day), isocarboxazid (30 mg. per day) and reserpine, reserpine 2, and, finally, placebo 2. The average daily excretions of tryptamine and total indole-3-acetic acid were, respectively, 118 μ g. (range 39 to 585 μ g.) and 18.1 mg. (range 6.3 to 54 mg.), both figures being adjusted to a daily protein intake of 100 g. Reserpine therapy alone did not affect these average values. The average urinary tryptamine level was significantly higher during administration of placebo 2 than during administration of placebo 1. Tryptamine output in 6 patients with acute psychosis was found to be more than twice as high as in 17 patients (studied for a longer period of time) in whom the psychosis was apparently inactive. In 2 patients with very active psychosis the tryptamine output over 10 days averaged 416% of that of the inactive group. Similar but less pronounced changes were obtained for indole-acetic acid excretion. [Data for individual patients are not given.]

The authors conclude as follows: "Our most striking observation was a correlation between the excretions of tryptamine and total indole-3-acetic acid with the degree of

psychotic activity; both indoles attained increasingly high abnormal levels with augmentation in the severity of the psychosis, but reduction of indoles toward or to normal levels occurred with improvement of the mental state. Each of the two different biochemical patterns, the one occurring with activation of the psychotic symptoms and the other with a reduction of psychotic activity, retained its distinctive features whether or not reserpine was administered."

R. Rodnighi

TREATMENT

1121. Historical Aspects of Electroshock Therapy, Electrical Current Modifications, Treatment Techniques and Some Electroencephalographic Observations

D. GOLDMAN. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 210-215, April, 1962. 6 figs.

When Cerletti and Bini introduced electric convulsion therapy (E.C.T.) they used a controlled and measured sine wave current delivered from the commercially supplied electric lines. Various modifications in technique have been made since that time. The current has been rectified and only a brief stimulus current used; in the "glissando" technique and in electronarcosis other modifications of the current supply are employed. The author reports electroencephalographic (EEG) observations made during use of the different types of current and treatment technique. The varieties of current and treatment methods are illustrated diagrammatically. It is shown that E.C.T. with sine wave current given even at 2-week intervals maintains EEG changes that subside completely within 4 weeks of the last treatment. With "brief stimulus" therapy the EEG changes subside very rapidly after cessation of treatment and can be produced on one side of the brain only, if a single active electrode is used. Electronarcosis produces EEG effects similar to those of classic electroshock, but the changes are less intense and subside rapidly within 4 weeks of the last treatment.

B. M. Davies

1122. Electroconvulsive Therapy—Electrostimulatory or Convulsive Therapy?

J.-O. OTTOSSON. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 216-220, April, 1962. 1 fig., 19 refs.

Electric convulsion therapy (E.C.T.) was introduced into psychiatry as a technical modification of Meduna's pharmacological convulsion therapy. It has been assumed that the therapeutic agent in both methods is the grand-mal seizure. Lately, however, the electrical stimulus has been held to have the more fundamental effect of stimulating certain brain centres, the seizure being regarded as therapeutically irrelevant and serving only as a signal that the electrical stimulation has been strong enough. Opinions have differed on whether the memory disturbances that may follow E.C.T. are due to the seizures or to the electrical stimulation.

This paper from Karolinska Sjukhuset, Stockholm, describes experiments designed to determine whether the effects of E.C.T. are due to the seizure or to the electrical stimulation. The experimental design comprised variation of the former while the latter was constant, and vice versa, lignocaine being used to vary seizure activity. Three groups of patients were compared. In the first group seizures were induced by stimulation a little above threshold for a grand-

mal seizure and in the second group by 2 to 3 times that stimulus; in the third group the stimulation was little above the threshold but seizure activity was modified by lignocaine. It was in the third group that therapeutic effectiveness (assessed in cases of endogenous depression) was the least satisfactory. The author concludes from his findings that the action of E.C.T. in relieving depression is associated with seizure activity in the brain stem. Memory disturbance was shown to be largely due to a direct non-seizure effect of the electric current. The therapeutic implication of this research is that to minimize memory disturbance no more electrical energy should be used than is necessary to induce grand-mal seizure, although sub-seizure doses, which are therapeutically less effective, must be avoided.

B. M. Davies

1123. The Mode of Action of Convulsive Therapy: the Neuropsychologic-adaptive View

M. FINK. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 231-233, April, 1962. 10 refs.

It has now been established that electric convulsion therapy (E.C.T.) leads both to measurable changes in the electroencephalogram (EEG) and to changes in the patient's behaviour, and that systematic relationships exist between these two types of change. The changes produced in the brain by repeated seizures are reflected in the development of EEG slow-wave activity. This activity is heightened by intravenous administration of thiopentone and decreased by intravenous administration of atropine, hyoscine, and lignocaine. Subconvulsive treatments, on the other hand, usually produce no measurable EEG change and no change in behaviour.

The author, working at Hillside Hospital, Glen Oaks, Long Island, New York, detected no differences—electrical, psychological, or clinical—between patients who had had electrically induced seizures and those in whom seizures had been induced by chemical methods. The theory that he finds most useful in explaining the relation of brain change to clinical improvement is that E.C.T. produces neuropsychological alterations which are the cerebral basis for altered behavioural adaptations, moulded by personality variables and sustained by environmental tolerances.

B. M. Davies

1124. A Comparative Investigation of Isocarboxazid and Imipramine in Depressive Syndromes

T. ROTHMAN, H. GRAYSON, and J. FERGUSON. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 234-240, April, 1962. 11 refs.

A double-blind study was carried out at the Neuropsychiatric Hospital, Veterans Administration Center, Los Angeles, to determine the comparative efficacy of isocarboxazid, imipramine, and a placebo in the treatment of depression. An experimental design was used which prevented bias or extraneous non-pharmacological factors from influencing the evaluation, which was made clinically and on a number of psychiatric rating scales which assessed symptoms and mental and motor speed. The results, analysed statistically, cast doubt on the supposition that these two reputedly antidepressant drugs are significantly more effective therapeutic agents for depressive states than a placebo. Favourable changes reported in trials of antidepressant drugs may be brought about by non-pharmacological factors.

B. M. Davies

Dermatology

1125. **Dermatology in Uganda, 1931-1941.** (Als Dermatologie in Uganda, 1931 bis 1941)

L. J. A. LOEWENTHAL. *Dermatologische Wochenschrift* [Derm. Wschr.] 145, 481-492, May 12, 1962. 9 figs., 19 refs.

The author, writing from the South African Institute of Medical Research, Johannesburg, describes his experience of dermatological practice in Uganda between 1931 and 1941. Apart from leprosy, smallpox, typhus, plague, and trypanosomiasis, with which he was not concerned, the commonest affections were caused by treponemata, parasites, and superficial fungi. In framboesia, which has points of similarity with the Central American disease, pinta, there is a direct-contact primary lesion closely resembling the primary syphilitic chancre, while the chief late manifestation is leucoderma. In syphilis, which is under better control now than it was early in the century, the primary lesions are often multiple; the second stage is reached rapidly and the commonest lesions, especially in the negro, are annulopustular; in the third stage, aortitis and aneurysms, developing within a few years of the initial infection, are characteristic. Infection with Ducrey's bacillus is frequently associated with syphilis, as also is gonorrhoea, which tends to produce extensive strictures and scarring. Tropical ulcers occur only in malnourished subjects living in unsatisfactory sanitary conditions, particularly if the diet is poor in meat. Avitaminoses are frequently encountered, one of the commonest being a papular type of keratoderma, with xerophthalmia and night-blindness, due to lack of vitamin A. Castellani's tinea tropicalis perstans is seen; it runs a rapid course and produces annular destruction of beard and scalp hair within a few months, leaving a scarred central patch of alopecia with a peripheral fringe of stunted white hairs—leucotrichia cicatrisans.

Of the parasitic infections, onchocerciasis is the most deforming, usually producing the so-called "alligator" skin. In lymphostatic verrucosis (the disease which Robles described as "pseudolepra") multiple warty lesions appear on the lower limbs and chronic lymphoedema develops, ultimately progressing to pseudoscleroderma. This condition may affect the stump after amputation of a leg. Among other unusual diseases mentioned is one of the first cases of Kaposi's haemorrhagic sarcoma to be observed in a negro.

Allene Scott

1126. **Beta Radiation in Dermatological Treatment.** (Le radiazioni beta in terapia dermatologica)

G. LOVERA. *Minerva medica* [Minerva med.] 53, 997-1001, April 4, 1962. 28 refs.

The use of beta rays in the treatment of dermatological conditions is discussed in this paper from the University of Turin. The source of such radiation may be an electron accelerator or radioisotopes. Radioactive phosphorus has been employed (for example, in the treatment of haemangiomas), but the present author used radioactive strontium and radioactive yttrium. The former has a long half-life (25 years), but its electrons have an energy value of only 0.65 MeV. and therefore have only slight powers of penetra-

tion and are valueless in treatment. On the other hand radioactive strontium provides a source of radioactive yttrium, an isotope with a short half-life (62 hours) capable of emitting beta rays of high energy (2.23 MeV.).

Each plate used was 12 mm. in diameter and contained 50 mc. of radioactive strontium. The back and sides of the plate were made in such a way as to be impenetrable to beta radiation from the yttrium. The front (applied to the skin) was made of a very thin (0.3 mm.) leaf of nickel steel. The output was found to be 3,140 r. per minute with the plate in contact with the skin and 1,500 r. per minute with a filter applied to the surface. This form of treatment has been under trial for 3 years. The chief indications have been Paget's disease of the nipple, Bowen's disease [a variety of endo-epidermal carcinoma], senile keratoses, lentigo maligna, erythroplasia of Queyrat, some types of basal-cell carcinoma, haemangiomas, plane warts, and certain other conditions.

[Details of dosage are not given and the results are expressed in general terms only, but the author considers that the method described is an important advance in radiotherapy.]

S. T. Anning

1127. **Studies on Basophil Leucocytes with Special Reference to Urticaria and Anaphylaxis.** [Monograph, in English]

H. RORSMAN. *Acta dermato-venereologica* [Acta dermatol. (Stockh.)] 42, Suppl. 48, 1-20, 1962. Bibliography

1128. **Incidence and Bacteriology of Erythrasma**

I. SARKANY, D. TAPLIN, and H. BLANK. *Archives of Dermatology* [Arch. Derm.] 85, 578-582, April, 1962. 4 figs., 1 refs.

In an earlier paper (*J. Amer. med. Ass.*, 1961, 177, 130) the authors reported a study which showed that erythrasma is an infection of the skin due to a diphtheroid member of the genus *Corynebacterium*, and described an additional diagnostic aid—namely, the red fluorescence of affected areas under Wood's light. In the present paper, from the University of Miami School of Medicine, Florida, they discuss the incidence and bacteriology of the disease.

All social classes and age groups and males and females may be affected, but the classic genito-crural form occurs predominantly in males, in whom it is usually asymptomatic. The generalized form is more prevalent in tropical or subtropical regions, where it is most commonly seen in middle-aged negro women. Erythrasma of the webs of the toes however, appears to occur with equal frequency in hot and temperate climates; available figures show that approximately one-quarter of the population in Miami and in London are affected. A culture medium consisting of 78% tissue culture medium 199, 20% foetal bovine serum, and 2% agar seemed to provide optimal growth of the Gram-positive bacilli, which were 2 μ to 3 μ in length and 0.5 μ to 1 μ in diameter. The coral-red fluorescence produced by the colonies in culture appears to be a porphyrin, which is soluble in water but insoluble in ether or chloroform.

Sensitivity studies showed maximum inhibition with erythromycin and less inhibition with chloramphenicol, tetracycline, neomycin, penicillin, and dihydrostreptomycin. There was no inhibition with sulphadiazine or "gantrisin" sulphafurazole.

Benjamin Schwartz

129. The Systemic and Local Treatment of Dermatophytoses with Griseofulvin. [In English]

3. SYLVEST. *Acta dermato-venereologica* [*Acta derm.-enercol.* (Stockh.)] 42, 139-148, 1962. 40 refs.

The author describes 110 cases of dermatophytosis given griseofulvin by mouth and 50 cases of this condition in which griseofulvin was applied locally.

The oral dosage of griseofulvin was 250 mg. 4 times a day for adults and correspondingly less for children. Most of the patients were kept under observation for several months, and more than half for over a year. Tinea of the hands and feet did not respond well, only 3 of 23 patients being cured, whereas 74 of 82 patients with tinea in other sites were cured after treatment lasting from 8 to 105 days. Only one of 8 patients with tinea of the nails was cured, and then only after removal of the nails. Infection of hair responded more slowly than infection of glabrous skin. The poor results obtained in the hands and feet are considered to be due to profuse sweating and to lack of hair follicles, around which griseofulvin is concentrated. *Trichophyton rubrum* was not easily eradicated, but most cases of *T. verrucosum* infection responded. Side-effects consisted chiefly of headache at the beginning of therapy and, in a few cases, nausea, vertigo, and itching. There were no blood dyscrasias.

Of the 50 patients given local treatment with a 1% solution of griseofulvin in alcohol only 15 responded well. Topical application was thus less effective than oral administration. The addition of prednisolone to the lotion did not improve the response.

E. H. Johnson

1130. Progressive Systemic Sclerosis like Scleroderma

G. P. RODNAN and R. H. FENNELL JR. *Journal of the American Medical Association* [*J. Amer. med. Ass.*] 180, 665-670, May 26, 1962. 6 figs., 23 refs.

The authors of this paper from the University of Pittsburgh School of Medicine describe 4 patients who died from progressive systemic sclerosis, of whom 3 had no scleroderma and one had only minimal skin disease. The first patient, a 51-year-old man, complained of vomiting, abdominal pain, and diarrhoea of 6 months' duration and a weight loss of 50 lb. (22.67 kg.). At laparotomy only thickening and dilatation of the jejunum and enlargement of the lymph nodes were found. Postmortem examination showed severe sclerosis of the entire gastro-intestinal tract, but no involvement of the skin. The second patient, a 69-year-old housewife, had had increasing regurgitation of food over a period of one year. She also had nocturnal dyspnoea and some arthritis. She died from aspiration pneumonia and postmortem examination revealed dilatation of the oesophagus with extensive sclerosis of the lung, myocardium, and entire alimentary canal. The third patient, a 59-year-old housewife, had dyspnoea on exertion, swelling of the ankles, and signs of hypothyroidism, anaemia, and hypergammaglobulinaemia. Pyelonephritis subsequently developed. At necropsy sclerosis involving the myocardium, pericardium, oesophagus, and synovium was found; there were also changes typical of Sjögren's syndrome and of Hashimoto's

thyroiditis. The fourth patient, a 71-year-old female, had dyspnoea, orthopnoea, and cough. On either side of the chest there were two patches, 4x6 cm. in diameter, which were shiny and thickened with depigmentation. Postmortem examination showed thickening of the lower portion of the oesophagus with fibrosis of the small intestine and sclerosis of the myocardium.

These cases are of special interest, since in most instances progressive systemic sclerosis is diagnosed on the basis of typical skin disease.

E. H. Johnson

1131. Treatment of Mycosis Fungoides with Cyclophosphamide

E. J. VAN SCOTT, R. AUERBACH, and W. E. CLENDENNING. *Archives of Dermatology* [*Arch. Derm.*] 85, 499-501, April, 1962. 3 figs., 4 refs.

The results obtained with cyclophosphamide in 10 proven cases of mycosis fungoides and one case of lymphosarcoma are reported in this paper from the National Cancer Institute, Bethesda, Maryland. The condition was advanced, with cutaneous tumours or elevated plaques in all cases.

Cyclophosphamide was given in a dosage which varied between 50 and 300 mg. daily and was continued in each case until leucopenia or thrombocytopenia developed. Administration was resumed when the blood count returned to normal. During treatment varying degrees of hair loss were detectable in all patients and some noted mild nausea or anorexia. The tabulated results show that a significant remission of the disease occurred in 5 of the 11 patients, with disappearance of erythema and resolution of the elevated plaques and tumours. In a further 3 patients the decrease in size of lesions was only temporary in spite of continued treatment. There was no response in the remaining 3 patients.

The authors emphasize the need for close laboratory supervision of patients during cyclophosphamide therapy.

Benjamin Schwartz

1132. Results of X-ray Treatment of Chronic Perionychia. (Roentgentherapie delle perionissi croniche e suoi risultati)

G. SANNA. *Radiobiologia, radioterapia e fisica medica* [*Radiobiol. Radioter. Fis. med.*] 17, 54-70, Jan.-Feb. [received July], 1962. 4 figs., 15 refs.

This paper from the University of Parma describes 31 cases of perionychia treated by irradiation after intensive medical treatment had failed. The technique used was: 100 kV., filter of 2.5 mm. Al, focus skin distance 30 cm.; doses of 80 to 120 r. according to chronicity every 2 or 3 days to a total of 700 to 1,000 r.; the field extended down to the joint between the second and third phalanges. Recurrences were treated, after an interval of at least 2 months, with doses at weekly intervals; if a third course was needed only 2 or 3 doses were given every 10 to 15 days. Complete cure resulted in 24 cases and great improvement in 7; there were no failures.

All the patients were seen again after 3 months and most of them after one year. Recurrences were seen in 4 who had disobeyed instructions to avoid water. The author considers that x-ray treatment should be begun at an early stage and not regarded as a last resort. Even the newer medical agents such as griseofulvin do not replace x rays; the two methods should be used together, as their action is synergistic.

J. Walter

Paediatrics

1133. Otitis Media in Premature Infants: a Histopathologic Study

M. S. McLELLAN, J. P. STRONG, Q. R. JOHNSON, and J. H. DENT. *Journal of Pediatrics* [J. Pediat.] 61, 53-57, July, 1962. 1 fig., 5 refs.

Although reports on otitis media in newborn infants have appeared periodically since the 19th century, these have not dealt primarily with premature infants. The present authors have made a histopathological study of the prevalence of otitis media in premature infants whose birth weight ranged from 1,001 to 1,500 g. Among a group of 124 such infants admitted to the Charity Hospital of Louisiana, New Orleans, there were 40 deaths. An examination was made of 49 specimens of the petrous portion of the temporal bone, including the middle ear and ear-drum, obtained from 28, chosen at random, of the 40 necropsies. The specimens were removed *en bloc* and placed in neutralized formalin; after fixation, they were decalcified, embedded in paraffin, sectioned frontally, and stained with haematoxylin and eosin. Examination revealed an exudate of polymorphonuclear leucocytes in the middle-ear cavity in 28 of the 49 specimens. Of 21 cases in which both temporal bones were examined, purulent exudate was found bilaterally in 9 and unilaterally in 6; of 7 cases in which only one petrous bone was examined, exudate was found in 4. Although the presence of purulent exudate consisting of neutrophil granulocytes and a few macrophages in the middle-ear cavity was the only diagnostic criterion, cornified squamous epithelial cells, proteinaceous fluid, and erythrocytes were often also present. The substantia propria underneath the epithelial lining was usually hyperaemic and interstitial haemorrhage was observed occasionally. Infiltration of underlying connective tissue with neutrophil granulocytes was seen in most of the cases in which exudate was abundant; ulceration of the lining epithelium was observed occasionally. The exudate did not usually contain fibrin, a finding which may suggest an altered tissue response to infection in the newborn. The authors conclude that infection may play an important part in the morbidity and mortality of premature infants.

R. G. Meyer

1134. The Treatment of Chronic Nutritional Disturbances in Children with the Secretion of the Allotrophic Glands of Bees.

(Применение препарата пчелиного маточного молочка у детей с хроническими расстройствами питания)
E. M. FATEEVA and N. I. ROŠAL'. *Педиатрия* [Pediatriya] 41, 15-19, April, 1962. 1 fig.

Working bees feed their queen and larvae with the secretion of their allotrophic glands. The reigning queen as well as the larvae of future queens receive large quantities of this secretion, which the Russians call "queen's milk", with the result that the queen is capable of producing her own weight of eggs a day. This secretion was isolated and given to children with chronic nutritional disturbances in doses of 5 mg. a day either in the form of sublingual tablets or as suppositories. Of 40 children thus treated 35 greatly improved. There were no side-effects.

A. Orley

1135. Non-specific Mesenteric Adenitis in Children. (Неопищеческие мезадениты у детей)

A. G. EC and V. D. SURKOV. *Советская Медицина* [Sovetsk. Med.] 25, 96-99, May, 1962. 5 refs.

The aetiology, pathogenesis, and clinical features of acute mesenteric adenitis are discussed. In 17 cases admitted to hospital between 1955 and 1960 the diagnosis before admission was appendicitis in 12, helminthiasis in 4, and influenza in one. The cases were acute and most of them occurred in late autumn and early spring. The abdominal symptoms were often preceded for 3 to 4 days by upper respiratory catarrh and accompanied by herpes labialis. Leucocytosis was present in 12 cases, but was slight in 5. The erythrocyte sedimentation rate was approximately parallel to the leucocytosis. In some cases the enlarged lymph nodes were palpable. The authors state that tuberculous infection must be excluded by the usual tests before non-specific adenitis can be diagnosed. The diagnosis from acute appendicitis is difficult and is usually made on the operating table. The condition should be kept in mind when abdominal symptoms are present in any patient of tender years. Of the 17 patients 8 were aged 3 to 7 years, 7 between 8 and 10, and 2 between 11 and 14. If appendicitis can be excluded, treatment is conservative, by rest and by administration of antibiotics and a diet rich in vitamins. The authors gave 50,000 to 100,000 units of penicillin intraperitoneally. Of their 17 patients, 10 were operated on. The progress of the disease, in the authors' view, is unaffected by appendectomy, and the symptoms are liable to recur whether surgical or conservative treatment is given.

L. Firman-Edwards

1136. Results of Surgical Treatment in Hirschsprung's Disease

J. KOSTIA. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 167-168, April, 1962. 3 refs.

This is a report of the results of surgical treatment of Hirschsprung's disease at the Children's Hospital of the Helsinki University Clinic.

Since 1948, 89 patients with aganglionic megacolon have been treated, 68 with Hirschsprung's disease and 21 in whom the anomaly developed with anal atresia. The follow-up period varied from less than one year to over 10 years; 9 patients with Hirschsprung's disease died in early infancy. Operation was performed on 59 children, most of them under 2 years of age. The operations were abdomino-anal resection (Swenson), abdominal resection (Rehbein), and abdomino-perineal resection (Duhamel). A decompressive colostomy was carried out in 15 cases. There was no operative mortality. In the 28 cases treated by the Swenson technique there was a high incidence of postoperative complications, mostly due to leakage at the anastomosis. These complications are listed as: pelvic abscess (4), peritonitis (1), septicaemia (2), recto-urethral fistula (1), anastomotic stricture (6), and intestinal obstruction due to adhesions (4); there were 3 deaths. The results of the Swenson procedure were: symptomless 18 patients, recurrence 2, constipation 3,

soiling 2. In the 8 cases treated by abdominal resection (Rehbein) there were no deaths and no postoperative complications. The results were: symptomless 5, recurrence 1, and soiling 2. In the 26 cases treated by abdomino-perineal resection (Duhamel) the postoperative complications were: intussusception 1, mucosal prolapse 4, septum rectale 4; and the results were: symptomless 15, soiling 10, and one death.

Andrew M. Desmond

1137. Cholecystitis and Cholelithiasis in Children

S. SÖDERLUND and B. ZETTERSTRÖM. *Archives of Disease in Childhood* [Arch. Dis. Childh.] 37, 174-180, April, 1962. 3 figs., 40 refs.

Between 1950 and 1961 a total of 60 children, aged 6 to 15 years, with gall-bladder disease were operated on at Kronprinsessan Lovisas Barnsjukhus, Stockholm. In the present paper the series, which is claimed to be the largest to be reported in the literature, is analysed.

Of the 60 patients (3 male and 57 female) only 5 were younger than 11 years. Underlying conditions, such as haemolytic anaemia (3) and malformations of the gall-bladder (3), were uncommon. Stones in the gall-bladder and cholecystitis were the usual pathological abnormalities. The symptoms, which were similar to those seen in adults, had been present for up to 10 years in some of the patients. Diagnosis of the condition was often difficult. Cholecystography was found to be the most useful investigation and is recommended for children, especially girls, with vague abdominal symptoms. In all the cases treatment was surgical—namely, cholecystectomy. Follow-up examination revealed that the results were eminently satisfactory. In only 3 children were mild residual symptoms present.

[It is somewhat difficult to assess the incidence of gall-bladder disease in Swedish children (most of those in the present series were overweight) because no indications of the probable population at risk are given.] John Fry

1138. Temporal Lobe Syndrome in Children. A Longitudinal Review

P. F. BRAY. *Pediatrics* [Pediatrics] 29, 617-628, April, 1962. 11 figs., 24 refs.

Twenty children with a well-defined temporal lobe electroencephalographic focus were studied for a period averaging 7 years. A careful search was conducted for etiologic factors, and correlation of psychological patterns with electroencephalographic findings was carried out. In addition neurologic deficit, psychometric findings and social adjustment were studied.

A genetic etiology was suspected in half of the patients on the basis of a clear history of epilepsy, a severe psychiatric disturbance, or the presence of a temporal lobe focus in a close relative, although a familial incidence was well documented in only 3 of the 10 patients. Hippocampal sclerosis secondary to herniation of the temporal lobe uncus and compromise of its circulation was thought to be etiologic in 2 small premature infants who experienced marked neonatal asphyxia, and in one child who suffered a severe head injury. A cystic astrocytoma had caused focal motor seizures in one patient for a 7-year period prior to its total removal.

A wide pattern of psychologic diagnosis was noted, ranging from 4 normal to 6 psychotic, 4 hyperactive, 4 neurotic and 2 retarded children. All psychotic children had either

a unilateral midtemporal spike focus or spike foci arising independently in both temporal lobes. Three of the 4 patients with bilateral abnormalities were psychotic, a finding that might be related to the bizarre behavioral changes in animals which have undergone bilateral temporal lobectomy. Neurologic abnormalities were restricted to mild speech disorders in 2 patients with normal intellect, a finding possibly related to the expressive language functions centered in the temporal lobe.

Eighteen of the 20 patients were functioning in the normal intellectual range, 2 were mentally deficient and the other 3, although functioning in the subnormal range, had normal intellectual potential. Social maladjustment, resulting from serious behavioral and psychological seizures, affected 15 of the 20 patients in the early phase of the study. Follow-up examinations revealed improvement in 6 of the socially handicapped patients. This improvement occurred with all types of temporal lobe electroencephalographic abnormality, excluding those with anterior temporal spike activity.

All 11 patients who had psychomotor seizures were incompletely controlled after vigorous, prolonged attempts at medical management. Grand mal attacks were seen in 15 of the patients and were easily controlled. Surgery for the relief of seizures was performed in 3 patients and benefited only the one whose tumor was removed. The other 2 patients, who underwent limited subpial resections, showed no improvement.—[Author's summary.]

1139. The Electroencephalogram in Children with Intracranial Tumors and Seizures

J. G. MILLICHAP, R. G. BICKFORD, R. H. MILLER, and R. E. BACKUS. *Neurology* [Neurology (Minneapolis)] 12, 329-336, May, 1962. 4 figs., 9 refs.

Of 291 children treated for intracranial tumour at the Mayo Clinic in 1950-1, 50 (17%) had seizures, and in 44 of these the electroencephalogram (EEG) was recorded. In 31 of the 50 children the tumour was supratentorial and in 19 it was infratentorial. The average ages at onset of the seizures and at diagnosis of the tumour were 4.9 and 6.7 years respectively in the supratentorial cases and 4.8 and 5.1 years in the infratentorial cases.

Of the patients with supratentorial tumours the EEG was abnormal in 27 and normal in one, while of those with infratentorial tumours it was abnormal in 13 and normal in 3. The EEG was of value in locating the tumour in 75% of the supratentorial growths and in 88% of cases in which the cortex was involved. Only 7 of the 16 patients with infratentorial tumours in whom the EEG was recorded had the generalized dysrhythmia, maximal in the occipital regions, which is associated with posterior fossa lesions. The authors comment that focal abnormalities elsewhere in 5 patients were not accompanied by neurological signs suggestive of a secondary growth. Only 4 of their patients had the typical episodic opisthotonos and respiratory irregularities of a posterior fossa tumour. The value of the EEG in differential diagnosis between tumour and static lesion was less than its value in locating the growth. Only 57% of the supratentorial tumours gave a delta pattern indicative of an expanding lesion.

[There are obvious limitations in analysing only one application of a diagnostic procedure. A corresponding analysis of children with focal abnormalities but no tumours is desirable.] N. S. Alcock

Medical Genetics

1140. Paternal Age in Mongolism

L. S. PENROSE. • *Lancet* [*Lancet*] 1, 1101, May 26, 1962. 17 refs.

The author, at University College, London, has reviewed the literature concerning the role of paternal age in mongolism. Compared with the age of the mother, the father's age is generally regarded as unimportant in the production of a mongol infant. Nevertheless, a few instances have been noted in which the father was much older than the mother, and it would appear that this difference in parental age is a feature of mongolism with somatic chromosomal fusion of the type (21):(21 or 22). In each of 8 such reported cases the father's age was greater than the mother's; the average ages were 42.5 and 33.4 years respectively and, although both are significantly greater than the averages expected from appropriate controls (31.7 and 28.0 years respectively), the difference observed for mothers can be accounted for by the natural association in the ages of married partners. In contrast, an analysis of parental ages of 14 reported cases of mongolism with somatic chromosomal fusion of the type (13, 14; or 15):(21) revealed no important disparity. The average ages of the fathers and mothers when the affected children were born were 30.3 and 27.6 years respectively, compared with 31.7 and 28.0 years for controls. A possible explanation of the occasional observation of excessively high paternal age is selection which acts against unbalanced gametes, ova, and sperms carrying the (21):(21 or 22) chromosomal fusion, and which is ineffective against sperms from older fathers.

E. A. Cheeseman

1141. Mongolism in Three Siblings with 46 Chromosomes

L. ATKINS, M. A. O'SULLIVAN, and C. V. PRYLES. *New England Journal of Medicine* [*New Engl. J. Med.*] 266, 631-635, March 29, 1962. 6 figs., 22 refs.

Mongolism in siblings is a relatively rare event. The authors report from Harvard Medical School, Boston, a family containing 3 mongols, 2 males and a female, now aged 34, 25, and 29 years respectively. The mother had no other pregnancies, and there was no other known mongol in the paternal or maternal families. The father was 31 and the mother 26 years old at the birth of the first patient. Chromosome studies showed that the mother had 45 chromosomes with a probable 15/21 translocation, that the father was of normal karyotype, and that the 3 mongol offspring had 46 chromosomes with a probable 15/21 translocation. Urinary indole-acetic acid excretion in all 3 patients and their parents was found to be normal, but one patient and both parents had a slightly raised excretion of indican. The urinary chromatograms and values for serum protein-bound iodine and urinary 17-ketosteroid excretion were within normal limits, except in one patient in whom the 17-ketosteroid excretion was low.

In the institution where the three patients live there was a total of 370 mongol individuals. In this population there were 4 instances of 2 mongol members in one family, the maternal age at the birth of the first child ranging from

32 to 44 years. Chromosome studies of these 8 dually affected sibships showed regular 47-chromosome mongolism, with trisomy 21, in all.

C. O. Carter

1142. Chromosomal Translocations in Patients with Mongolism and in Their Normal Relatives

W. R. BREG, O. J. MILLER, and R. D. SCHMICKEL. *New England Journal of Medicine* [*New Engl. J. Med.*] 266, 845-852, April 26, 1962. 8 figs., 22 refs.

The authors, reporting from Yale University, New Haven, and Columbia University, New York, describe two families each containing a patient with Down's syndrome (mongolism) with 46 chromosomes and a probable 15/21 translocation. The two index patients, both male, were found during the examination of a series of 12 mongol children all born to mothers under the age of 29. In the first of the two families investigated the patient's mother and his normal brother (his only sib) were carriers of the translocation, but themselves had somatic chromosome numbers of 45; the patient was born when the mother was 28. In the second family the father was dead, but the mother and 3 sibs all had normal karyotypes.

C. O. Carter

1143. Ascertaining Genetic Carriers of Hereditary Spherocytosis by Statistical Analysis of Multiple Laboratory Tests

A. A. MACKINNEY JR., N. E. MORTON, N. S. KOSOWER, and R. F. SCHILLING. *Journal of Clinical Investigation* [*J. clin. Invest.*] 41, 554-567, March [received May], 1962. 5 figs., 28 refs.

Medical geneticists may have difficulty in making complete family studies of acholuric jaundice, both because the disease may be mild and because of the lack of well-defined diagnostic criteria. The authors of the present paper, at the University of Wisconsin Medical School, Madison, investigated 181 members of 26 families with hereditary spherocytosis. Four groups of subjects—namely, controls (volunteers from hospital staff and normal spouses of family members), normal family members, affected family members with intact spleens, and affected family members after splenectomy—were subjected to 12 laboratory tests, including spherocyte score, reticulocyte count, haemoglobin and bilirubin estimation, and fragility studies. Means and standard deviations for the 12 tests were calculated. Correlations of the tests individually indicated many significant interrelationships. It was established that, after study of the initial case, not more than 4 of the tests are required for the identification of family members with hereditary spherocytosis. Computer analysis of the data obtained gave a 97% accurate diagnosis and a higher incidence of the disease than in any other series of investigations. The incidence found in the families expected to have spherocytosis was 0.51 ± 0.042 with a slight but not significant excess of males.

[Large-scale statistical evaluation of multiple laboratory tests on patients is relatively new, and the paper deserves to be read by all interested in medical genetics, especially if they wish to study conditions in which diagnosis is difficult.]

I. Dunsford

Public Health and Industrial Medicine

1144. Food Poisoning Due to Turtle Flesh (a Study of 130 Cases)

V. K. PILLAI, M. B. NAIR, K. RAVINDRANATHAN, and C. S. PITCHUMONI. *Journal of the Association of Physicians of India [J. Ass. Phys. India]* 10, 181-187, April, 1962. 6 figs., 7 refs.

This paper from the Medical College, Trivandrum, Travancore-Cochin, India, describes 130 cases of poisoning caused by eating turtle. During the monsoon months of May to July turtles (*Eretmochelys imbricata*) are caught by trapping along the coast of South Kerala. They measure 2 to 4 ft. (0.60 to 1.22 m.) in length and each provides a day's food for 10 to 15 families. The usual method of preparation is to boil the turtle, throw away the water in which it is boiled, and then make a curry with the boiled flesh.

On May 27, 1961, five turtles were caught alive near the coastal town of Quilon, and one of them, which was shared among 12 families, proved poisonous. Of the individuals who consumed its flesh, 32 suffered severe or moderate illness and 98 had mild symptoms; in every one of these cases the flesh consumed had been prepared by boiling, but the water had not been "decanted". Where the preparation had included decanting no noticeable symptoms occurred in the consumers. The clinical features in the affected subjects included bilious vomiting, constipation, glossitis, drowsiness, coma, and, in 2 children, convulsions. There were 18 deaths, including the 2 children who had convulsions and 6 pregnant women (who aborted before death). In all the fatal cases death was due to respiratory paralysis. Necropsy was performed in 5 of the cases. The findings, which included ulceration from the mouth downwards, liver damage, and congestion in the floor of the fourth ventricle, are interpreted by the authors as evidence that the poison was both an irritant and a neurotoxin. J. Cauchi

1145. Intranasal Revaccination against Diphtheria. (Интраназальная ревакцинация против дифтерии. Сообщение I.)

I. E. ALATYRCEVA, F. B. KOLPAKHIN, N. F. AMETATEIROVA, V. N. ŠAROVSKAJA, A. I. DVORKINA, V. K. MEL'NIKOVA, and I. G. BERZON. *Вопросы Охраны Материнства и Детства [Vop. Okhran. Materin. Dets.]* 7, 29-32, April, 1962. 6 refs.

In an investigation in guinea-pigs and rabbits of immunization against diphtheria by intranasal instillation of pure concentrated diphtheria anatoxin it was found that 45 antitoxic units per ml. produced insignificant results. However, 150 to 400 units per ml. gave positive results in a number of guinea-pigs and rabbits. The method was then tried with the stronger solution (400 units per ml.) in 66 children, of whom 18 had titres of diphtheria toxoid below 0.03 unit. The children, who were aged from 9 to 10 years, were receiving their fourth revaccination. The dosage was 5 drops in each nostril daily for 3 days, the course being repeated 3 times at 12-day intervals. The response was not inferior to that obtained in 58 other children with immunization by

the subcutaneous route. There were no side-effects. The authors recommend further testing on a larger scale of this simple and painless method of revaccinating children.

L. Firman-Edwards

1146. Community-wide Use of a "Balanced" Trivalent Oral Poliovirus Vaccine (Sabin): a Report of the 1961 Trial at Prince Albert, Saskatchewan

H. E. ROBERTSON, M. S. ACKER, H. O. DILLENBERG, R. WOODROW, R. J. WILSON, W. K. ING, and D. R. E. MACLEOD. *Canadian Journal of Public Health [Canad. J. publ. Hlth]* 53, 179-191, May, 1962. 12 refs.

In the previous trials carried out elsewhere it was found that trivalent oral poliomyelitis vaccine containing equal amounts of all three types of virus produced an uneven antibody response, the response to Type-2 virus predominating. To determine whether this could be overcome by decreasing the proportion of the more infective Type-2 and Type-3 viruses, a trial of "balanced" trivalent vaccine was carried out in Prince Albert, Saskatchewan, a city of 23,000 inhabitants, between February 27 and March 7, 1961. In previous years some 99% of the children under 16 years and 65% of the adults under 40 in the city had received 3 or more doses of Salk vaccine. A single dose of "balanced" Sabin vaccine containing 1,000,000 TCID₅₀ (tissue culture infectious dose) of Type-1 poliomyelitis virus, 100,000 TCID₅₀ of Type-2 virus, and 316,000 TCID₅₀ of Type-3 virus was given to 23,711 subjects in 8 days. Specimens of faeces and blood were collected before and after vaccination from 583 subjects, mainly children and young adults. As a result of previous Salk vaccination only a small proportion were without detectable antibody before receiving the oral vaccine. Of 20 subjects without Type-2 antibody, all showed detectable antibody levels following the "balanced" vaccine, as did 48 subjects without Type-3 antibody. Of 38 without Type-1 antibody, however, 35 developed antibody following vaccination, but in 10 of these individuals the antibody titres were low. The poor response to the Type-1 component of the vaccine was reflected in the lower rate of excretion of Type-1 virus in vaccinated individuals in spite of the proportionately larger dose. This was considered to be due to interference with the Type-1 virus by the Type-2 virus, as prevaccination specimens of faeces yielded few "wild" enteroviruses. J. E. M. Whitehead

1147. New Quadruple Vaccine

D. S. DANE, G. W. A. DICK, D. I. H. SIMPSON, E. M. BRIGGS, J. MCALISTER, R. NELSON, and C. M. B. FIELD. *Lancet [Lancet]* 1, 939-941, May 5, 1962. 3 refs.

A trial of a new quadruple vaccine containing poliomyelitis, diphtheria, tetanus, and pertussis antigens, confined to infants aged 6 months or over who had had no previous immunization, was carried out in Belfast, Northern Ireland. Evaluation was made serologically on blood collected on the day the first dose of vaccine was given and one month after the third dose. Because of the long duration (3 months) of the study and the high-titre antibody responses

expected, faecal samples were examined monthly, and in some cases fortnightly, to detect any natural poliovirus infection that might have influenced the results. A standard cytopathic poliomyelitis neutralization test was also carried out.

All the infants given the vaccine "developed levels of antibody to poliovirus which were greatly superior to those which have resulted from primary immunisation with vaccines of the potency of those used up till now in the United Kingdom. The responses to the diphtheria, tetanus, and pertussis components of the vaccine were of the same order as those after immunisation with 'triple antigen'".

John Fry

1148. Epidemiology of an Outbreak of Tuberculosis Among School Children

E. F. H. ROGERS. *Public Health Reports* [Publ. Hlth Rep. (Wash.)] 77, 401-409, May, 1962. 1 ref.

An outbreak of primary tuberculosis which occurred in a school district within the territory of the New York State Health Department had its origin in an open case of pulmonary tuberculosis in a school bus driver, who took children to school regularly for some 6 months after the onset of his illness. He was suspected to have chronic pulmonary disease before his engagement. Of 266 children who rode with this driver, 85 (32%) gave a positive reaction to the tuberculin test, and active tuberculosis was diagnosed in 52 of these. There was close correlation between the incidence and severity of the tuberculous disease and the duration of contact with the driver. The incidence of positive tuberculin reactions among children attending the same schools, but who did not ride in the bus with the infective driver, was 1.8% and only 0.1% had active lesions. Extensive investigation among teachers and parents failed to reveal an alternative cause for the outbreak.

John Lorber

1149. An Outbreak of Sonne Dysentery in a Boarding School

W. I. GLASS and J. R. S. FINDON. *New Zealand Medical Journal* [N.Z. med. J.] 61, 199-211, April, 1962. 2 figs., 13 refs.

An outbreak of Sonne dysentery occurred between September 11 and October 14, 1961, among 286 boarders at a boys' school in Oamaru, New Zealand, the total number of cases being 130. The infection was probably introduced by a symptomless carrier, since 6 of these were discovered and there appeared to be no other source of the infection. At the beginning the outbreak was gradual, not explosive, but the infection spread rapidly and was over in 4½ weeks. The mode of spread seemed to be from hand-to-mouth through the handling of cut slices of bread which were stacked on the tables and freely handled by the boys. The extent and rapidity of spread reflected the grossly inadequate facilities for washing hands after using the toilet, and the gross overcrowding both in the dormitories and at the dining tables. Books, desks, pencils, door-knobs, and even toilet seats were not considered to be factors in the spread of dysentery because day boys were not affected. Treatment with sulphonamides was of little, if any, value; tests in 7 cases showed that the organism was insensitive to sulphonamides. Treatment with streptomycin by mouth in a dosage of 0.5 g. twice daily for 5 days was successful in 54 out of 68 cases. The most effective drug was framycetin; it was given to 31 patients, of whom 5 failed to respond to

a one-day course and 4 to a 2-day course. In all the 5 patients who did not respond to the one-day course there was rapid cure of the infection after a subsequent 2-day course. The authors emphasize the importance of personal hygiene in residential institutions for children and of adequate facilities for washing hands, as well as the need to avoid overcrowding.

H. Stanley Banks

INDUSTRIAL MEDICINE

1150. Toxicological and Physiopathological Study of Monobromo-trifluoromethane. (Étude toxicologique et physiopathologique du monobromo-trifluorométhane)

G. PAULET. *Archives des maladies professionnelles, de médecine du travail et de sécurité sociale* [Arch. Mal. prof.] 23, 341-348, June, 1962.

Monobromo-trifluoromethane (CF_3Br) has been proposed for use as a fire extinguisher. Tests for its toxicity to mammals, performed at the Faculty of Medicine and Pharmacy, Rennes, France, revealed that rats, mice, guinea-pigs, and rabbits were unharmed by exposure for 2 hours to an atmosphere containing 80% CF_3Br and 20% oxygen. Exposure to 50% CF_3Br for 15 consecutive days did not affect mice, rats, or guinea-pigs. Although after being heated to 800° C. the gas remained innocuous, heating above 950° C. rendered it strongly irritant.

J. M. Barnes

1151. Penicillamine as Lead-chelating Substance in Man

W. T. L. OHLSSON. *British Medical Journal* [Brit. med. J.] 1, 1454-1456, May 26, 1962. 12 refs.

Penicillamine (β - β -dimethylcysteine) has been found to increase the urinary excretion of copper in Wilson's disease. At the Central Hospital, Örebro, Sweden, the author has compared its effect on the urinary excretion of lead with that of calcium disodium ethylenediamine-tetraacetic acid (CaNa_2EDTA).

Penicillamine was given orally and intravenously to 8 men exposed in varying degree to the effects of lead. Intravenous administration of 1 to 3 g. of penicillamine in 500 ml. of physiological saline over 2 to 3 hours was followed by a rise in the urinary excretion of lead of about the same magnitude as that caused by CaNa_2EDTA . Only a moderate further increase in lead output was produced by doubling or trebling the dose of penicillamine on consecutive days. Oral administration of 0.3 to 1 g. of penicillamine daily also substantially increased the amount of lead in the urine. A possible synergistic action of penicillamine and CaNa_2EDTA was indicated by a considerable rise in lead excretion when both were given on the same day. An increase in the blood lead concentration was observed after each infusion of CaNa_2EDTA , but not after penicillamine. This suggests that the former mobilizes lead stored in the body.

Two cases were treated first with benzylpenicillin (2 mega units by mouth followed after 24 hours by intramuscular injection of the same dose for 2 days). With both forms of administration the urinary lead content increased slightly on the first but not the second day; the second dose, on the other hand, was followed by a notable but unexplained rise in the blood concentration of lead. Subsequent treatment with penicillamine led to a further rise in urinary lead content. No side-effects were observed in any of the 8 cases.

Ethel Browning

Anaesthetics

1152. Some Observations on the Use of Halothane ("Fluothane") in Paediatric Anaesthesia

M. BOOKALLIE and J. G. LOMAZ. *Medical Journal of Australia* [Med. J. Aust.] 1, 666-670, May 5, 1962. 5 figs., 20 refs.

At the Royal Alexandra Hospital for Children, Sydney, halothane anaesthesia was given to 603 infants and children aged from a few hours to 13 years. The surgical procedures were: general (in 144), cardiac and thoraco-abdominal (67), neurosurgical (73), plastic (112), orthopaedic (76), urological (84), and miscellaneous (47). Premedication was with atropine or, occasionally, hyoscine, usually combined with pethidine, pentobarbitone, "omnupon", or morphine. The apparatus used for children under 4 years, with either spontaneous or controlled respiration, was the Rees or the Medical Industrial Equipment modification of Ayre's T-piece, the necessary flow rate being at least twice the child's minute respiratory volume. For children between 4 and 8 years old a Magill semi-open circuit with the valve propped open, the Rubens non-rebreathing valve, or, where controlled respiration was required, the Waters canister, was used. For children over the age of 8 a circle absorption system was preferred. Anaesthesia was induced by injection of thiopentone sodium in 2.5% solution (4 to 8 mg. per kg. body weight) or by inhalation of nitrous oxide and oxygen, to which halothane was added from a "fluctec" Mark II vaporizer in gradually increasing concentration up to 2.5%. The patient was intubated (where indicated) following halothane inhalation, or suxamethonium chloride was given in a dosage of 0.25 mg. per kg. intravenously or 0.5 mg. per kg. intramuscularly or intralingually. Neonates were often intubated before the induction of anaesthesia. Halothane concentrations from 1% to 2% were used with spontaneous respiration, this concentration being reduced to 0.5 to 1% where controlled ventilation was produced. Diluted suxamethonium chloride by intermittent injection was the relaxant given to neonates and infants, and no dual block or marked bradycardia occurred. In older children gallamine triethiodide in an initial dosage of 0.5 mg. per kg. was used for relaxation, reversal being obtained if necessary with atropine 0.02 mg. per kg. preceding neostigmine 0.04 mg. per kg.

The authors discuss the use of halothane and recommend it on account of non-inflammability, absence of tracheal irritation and secretions, smooth induction, and rapid recovery. Bradycardia was not observed in children given atropine. The hypotension that occurred was moderate provided low concentrations of halothane were used, and did not cause anxiety, even in cardiac surgery and neurosurgical operations in the sitting position. Sinus tachycardia was fairly constant, but serious cardiac arrhythmias, such as the ventricular extrasystoles and ventricular tachycardia previously reported, were not observed in this series, apart from ventricular extrasystoles in 2 children operated on for ventricular septal defect. Muscle relaxation was poor under light halothane anaesthesia, and the authors advise the additional use of relaxants. Attention is drawn

to the loss of body heat that occurs in lengthy operations, and external warmth is recommended for infants up to 6 months old. During the production of surface hypothermia halothane proved satisfactory and could be discontinued until rewarming began. Halothane and oxygen passed to the oxygenator during perfusion with the heart-lung machine provided satisfactory maintenance of anaesthesia in concentrations of 0.5 to 1%, and was more satisfactory than the intermittent intravenous injection of anaesthetic agents.

In an addendum the authors state that a further 2,000 children have been anaesthetized with halothane without a fatality.

Raymond Vale

1153. Clinical Evaluation of Mepivacaine for Regional Anaesthesia

V. J. COLLINS and E. A. ROVENSTINE. *Archives of Surgery* [Arch. Surg.] 84, 680-685, June, 1962. 1 fig., 4 refs.

Mepivacaine hydrochloride has been used as the agent for nerve blocks for both therapeutic and surgical purposes in 829 patients, for a total of 1,084 blocks. This agent is effective in concentrations of 0.5% to 2%, and the 1% solution is apparently the most efficient. A survey of these clinical experiences shows that mepivacaine has a very rapid onset of action and a long duration of action. Satisfactory results were obtained in 95% of cases, demonstrating that under simple clinical circumstances it is a dependable agent, which shows superiority over lidocaine [lignocaine] and hexylcaine. Toxic reactions were minimal. Only 2 patients exhibited reactions which were cause for concern, and these were hypertensive in character. It is predicted that mepivacaine will be the popular local anesthetic agent during the next decade.—[Authors summary.]

1154. A Comparison between Methohexitone and Thiopentone as Induction Agents for Caesarean Section Anaesthesia

C. M. SLOM, L. FRANKEL, and R. A. HOLBROOK. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 316-326, May, 1962. 6 figs., 34 refs.

An analysis has been made [at King Edward VIII Hospital, Durban] of the condition of infants after delivery, when equipotent doses of methohexitone and thiopentone were used to induce anaesthesia for Caesarean section. The method of anaesthesia was in all other respects identical. The results indicated that there was less foetal depression following methohexitone than when thiopentone was used. The difference was not, however, statistically significant. Nevertheless it should be noted that in this series minimal doses of barbiturate were used. It is possible that if larger doses had been employed, a significant difference might have been observed.

The results in both series were most satisfactory and confirm that the utilization of a small induction dose of barbiturate, followed by a relaxant and controlled respiration with nitrous oxide and oxygen, causes less foetal depression than other forms of general anaesthesia.—[Authors' summary.]

1155. Alterations in Response to Somatic Pain Associated with Anaesthesia. - XI. Two Non-phenothiazine Anti-emetics: Cyclizine and Trimethobenzamide

R. M. NICHOLL, J. MOORE, and J. W. DUNDEE. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 287-289, May, 1962. 2 figs., 17 refs.

Analgesimetry studies were carried out on healthy subjects following the administration of two non-phenothiazine anti-emetics, cyclizine and trimethobenzamide. An increase in sensitivity to somatic pain followed the intravenous injection of clinically used doses of both drugs but this action was more marked and prolonged with cyclizine. Following intramuscular injection an anti-analgesic effect was present 60 to 90 minutes after cyclizine, but not after trimethobenzamide. The latter had no effect on pethidine analgesia.

The anti-analgesic action of cyclizine is associated with a very high incidence of excitatory phenomena following methohexitone and it is not recommended for use in pre-anaesthetic medication before methohexitone induction of anaesthesia.—[Authors' summary.]

1156. Tetrahydroaminoacridine. Clinical Use of a Cholinesterase Inhibitor in Conjunction with Succinylcholine. [In English]

D. BENVENISTE and V. DYRBERG. *Acta anaesthesiologica Scandinavica* [Acta anaesth. scand.] 6, 1-6, 1962. 4 refs.

Tetrahydroaminoacridine, a cholinesterase inhibitor, has been used to extend the neuromuscular blockade produced by succinylcholine in anaesthesia for 23 cases of abdominal hysterectomy. The study was designed to provide means for comparison with a previously established control series. Twenty-five mg. of tetrahydroaminoacridine, given immediately before induction of the anaesthesia, was found capable of reducing the necessary amount of succinylcholine during anaesthesia to 24% of that used in the control series.—[From the authors' summary.]

1157. Observations on the Prevention of Muscle Pains after Suxamethonium

D. C. WHITE. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 332-335, May, 1962. 17 refs.

The incidence of muscle pains produced by suxamethonium in patients undergoing bronchoscopy was reduced from 50% to 28% by the prior injection of a 5-mg. dose of gallamine. The severity of the pains was also greatly reduced. To obtain this effect it was essential to allow time for the gallamine to act before giving the suxamethonium. Two minutes was allowed in this series [of patients at Castle Hill Hospital, Cottingham, Yorkshire]. Slow injection of suxamethonium did not significantly alter the incidence or severity of the pains.—[Author's summary.]

1158. Phenazocine ("Narphen") Used as an Adjunct to Anaesthesia

K. B. THOMAS. *British Journal of Anaesthesia* [Brit. J. Anaesth.] 34, 336-339, May, 1962. 1 fig., 4 refs.

An investigation has been made [at the Royal Berkshire Hospital, Reading] in 150 uncomplicated surgical cases in which a new analgesic, phenazocine, was used as an adjunct to anaesthesia. Premedication consisted of promethazine and/or chlorpromazine. Thiopentone was followed by a mixture of nitrous oxide and oxygen, and 0.5 to 1 mg. phenazocine was given intravenously (equivalent to 0.01 mg.

per kg. body weight). Twenty-five patients were also studied in whom oxymorphone ("numorphan") was similarly used, and the smoothness of the anaesthesia with phenazocine compared very favourably with this, and with pethidine.

No important effects on the cardiovascular system were found, but respiratory depression was noted and is discussed. Postoperative recovery was rapid and uneventful. The dosage is critical if respiratory depression is to be avoided, and the association of other drugs (such as cyclopropane) may produce enhanced depression of respiration.

Phenazocine appears to have a definite place in this type of anaesthesia.—[Author's summary.]

1159. Metabolic Acidosis: a New Approach to "Neostigmine Resistant Curarisation"

D. K. BROOKS and S. A. FELDMAN. *Anaesthesia* [Anaesthesia] 17, 161-169, April, 1962. 9 refs.

Biochemical and clinical evidence is presented [from Westminster Hospital, London] to show that metabolic acidosis produces a syndrome of central nervous system depression manifesting as impaired consciousness, respiratory depression and cardiovascular collapse.

The syndrome produced by metabolic acidosis closely resembles that described as "neostigmine resistant curarisation", but it can also be produced as the result of various pathological processes. The condition can be successfully treated by the infusion of sodium bicarbonate and a régime of treatment is suggested.—[Authors' summary.]

1160. The Effect of Atropine and Neostigmine on the Pulse Rates of Anaesthetised Patients

S. W. KEMP and H. J. V. MORTON. *Anaesthesia* [Anaesthesia] 17, 170-175, April, 1962. 2 figs., 3 refs.

This investigation was carried out at Hillingdon Hospital, Middlesex, on 50 patients who had undergone abdominal surgery under thiopentone-nitrous oxide-oxygen-curare anaesthesia with controlled respiration. At the end of the operation 25 patients were given 1.28 mg. of atropine followed after several minutes by 2.5 mg. of neostigmine, the other 25 patients receiving the atropine and neostigmine mixed together. Anaesthesia and controlled respiration were continued while the changes in pulse rate were taking place. This rate was recorded by means of a carbon microphone strapped to the thumb and connected to a kymograph.

It was found that after administration of atropine alone tachycardia developed and continued until the subsequent neostigmine began to take effect. The mean time to onset of tachycardia was 25 seconds with atropine alone and 28.4 seconds with the atropine-neostigmine mixture, this difference being significant. After atropine the mean time from onset of tachycardia to maximum tachycardia was 19.9 seconds and the corresponding figure for the mixture was 17.1 seconds; this difference is also significant. No patient in either group showed slowing of the pulse rate before the onset of tachycardia. Administration of the mixture was always followed by a short period of steady maximum tachycardia lasting a mean of 27.8 seconds before slowing started. The onset of slowing was gradual and became maximum in 5 to 12 minutes. The average increase in pulse rate caused by atropine alone was 41.5 beats per minute as against 37.3 beats per minute caused by the mixture.

Mark Swerdlow

Radiology

1161. **Fibrous Dysplasia of the Skull and Its Differential Diagnosis: a Clinical and Roentgenographic Study of 46 Cases** N. LEEDS and W. B. SEAMAN. *Radiology* [Radiology] 78, 570-582, April, 1962. 15 figs., bibliography.

The authors describe 46 cases of fibrous dysplasia of the skull seen at the Columbia-Presbyterian Medical Center, New York. The frontal bone is most frequently involved and then the sphenoid, the occipital and temporal bones being rarely affected. The serum alkaline phosphatase level may be raised, particularly in children and adolescents. Progression, which is slow, occurs only during the years of growth. Malignant change is rare; it was seen in only one case in the present series. Radiologically there are three main types of fibrous dysplasia—sclerotic, cystic, and mixed. The cystic type is most common in the vault and bulges the outer table outwards. The sclerotic type tends to involve the sphenoid wings and may be indistinguishable from meningioma; radioactive uptake studies may be valuable in the differential diagnosis. Other conditions causing sclerosis of the skull are briefly mentioned. *D. E. Fletcher*

1162. **Cerebral Abscess in Early Infancy. An Angiographic Study: (Der frühkindliche Hirnabszess im Angiogramm)** A. ISFORT and G. MENGES. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 522-530, April, 1962. 6 figs., 28 refs.

From the University Surgical Clinic, Münster, the authors report the angiographic findings in 15 cases of abscess of the brain (excluding otogenic abscesses), 2 of which were in children of school age (8 and 10 years respectively) and 4 in babies ranging in age from 4 to 10 months, the incidence in children thus being relatively high. Only angiography is of real diagnostic help, and encephalography is actually contraindicated. The clinical signs are variable and not specific. Admittedly the technique of injection is not easy.

The appearances in babies are conditioned by the softness of the skull, which tends to bulge out locally, so that there is no shift of the cerebral vessels to the opposite side. Nor is there crowding of the cerebral vessels round the abscess, but a "blush" in the capsule, due to its vascularity, may be seen. The blood circulation time is not reduced. The volume of a cerebral abscess in early infancy may be up to one-third of that of the brain. In older children the signs approach more and more the findings in adults, such as displaced cerebral vessels and a vascular "wall" round the abscess, but in these patients also the cerebral circulation time remains normal. *F. M. Abeles*

1163. **Roentgen Findings in Terminal Bronchiolar Carcinoma** R. D. KITTREDGE and R. S. SHERMAN. *American Journal of Roentgenology, Radium Therapy, and Nuclear Medicine* [Amer. J. Roentgenol.] 87, 875-883, May, 1962. 6 figs., 34 refs.

The results are reported of a study of the radiological appearances in 36 cases of histologically proven terminal bronchiolar (alveolar-cell) carcinoma seen at the Sloan-

Kettering Center for Cancer and Allied Diseases, New York. Radiologically, 4 types were recognized. (1) The nodular form. In 18 cases there were single, well-circumscribed nodules, the diameters of which varied from 1.5 to 10 cm., being less than 3 cm. in 14 cases. Most of the nodules were spherical and clearly outlined. In 4 cases poorly defined translucencies, 1 to 2 cm. in diameter, were scattered throughout the lesion, and it was considered that these may be to some extent specific of terminal bronchiolar carcinoma. The rate of growth of these tumours was usually slow. (2) The infiltrative form. The x-ray appearances of 9 tumours varied from a patchy, irregular density of 2 cm. diameter to areas of 8 cm. in diameter with shaggy borders. The course of these tumours was irregular, and diffuse involvement developed later in 2 cases. (3) The segmental form. Here there were segmentally situated areas of consolidation. Of the 5 patients with this type of lesion, 4 died within a year. (4) The unclassified form. In the 4 patients with this type the pattern of the lesion was more varied. In one there was patchy density in the right lung with a pleural reaction; another had bilateral hilar lymph-node enlargement with mediastinal masses and a lingular nodule; in the third the pattern was diffuse and bronchopneumonic; and in the fourth a single nodule with patchy pneumonia was present. Three of these patients died within a year.

Intrapulmonary dissemination and regional lymph-node involvement, the latter relatively late, usually preceded distant metastases. A skeletal survey was carried out in only about one-third of the cases, and lytic bone metastases were found in 4. The mediastinum was involved in one case and the pleura in one. *B. Golberg*

1164. **Radiological Appearances in Pulmonary Aspergillosis** B. GOLBERG. *Clinical Radiology* [Clin. Radiol.] 13, 106-114, April, 1962. 22 figs., 13 refs.

Cases of pulmonary aspergillosis may be classified in four groups: fortuitous, saprophytic, allergic, and septicaemic. The first group includes those cases in which the fungi are transient residents following inhalation. The saprophytic group contains cases in which the fungi are growing in a lung damaged by some other disease. The characteristic lesion is a mycetoma; 21 cases of this type have been seen at the Middlesex Hospital, London, associated with tuberculosis (5), emphysema and fibrosis (4), bronchiectasis (4), localized fibrosis (3), asbestosis (2), sarcoid (2), and carcinoma (one case). In 8 cases radiographs were available before and after the appearance of the mycetoma. In the allergic group the patients either are asthmatics who have the fungus as a persistent or recurrent allergen or suffer from allergic pulmonary aspergillosis (a distinct entity in adults without any previous history of asthma), often following exposure to hop manure or compost. The radiological appearance in both forms is of recurring patches of lobar or segmental atelectasis or consolidation moving to different parts of the lung. There were 12 such cases in the author's series.

The septicaemic or pyaemic type is rare; no cases of this type are reported. It occurs most frequently as a terminal

bronchopneumonia in association with agranulocytosis, leukaemia, or the prolonged administration of cytotoxic, antibiotic, or corticosteroid drugs. *D. E. Fletcher*

1165. Hodgkin's Disease: a Radiological Survey

A. M. H. FISHER, B. KENDALL, and B. D. VAN LEUVEN. *Clinical Radiology* [Clin. Radiol.] 13, 115-127, April, 1962. 25 figs., 34 refs.

One hundred and fifty-four unselected cases of Hodgkin's disease [seen at the Middlesex Hospital, London, since 1930] have been reviewed. The direct and indirect signs of adenopathy in the thorax and abdomen have been described. Bone can be invaded from local nodes or be affected independently of them. Both types of lesion are discussed. The patterns of invasion of lung parenchyma are classified and the invasion of other organs is mentioned.—[From the authors' summary.]

1166. Coronary Angiography in 100 Cases of Ischemic Heart Disease

B. NORDENSTRÖM, C.-O. OVENFORS, and G. TÖRNELL. *Radiology* [Radiology] 78, 714-724, May, 1962. 20 figs., 11 refs.

The authors recall that as recently as 1940 the contrast media available for cardiovascular examinations were relatively toxic. At that time selective angiocardiology and thoracic aortography had usually to be performed under general anaesthesia. In order to avoid the blur produced by the movement of respiration, the lungs were inflated and kept in an inspiratory position during exposure of the film. Better results were obtained when the examination was performed with moderate inflation of the lungs. In 1955 Boerema and Blickman (*J. thorac. Surg.*, 1955, 30, 129; *Abstr. Wld Med.*, 1956, 19, 255), in experiments on dogs, obtained better angiocardiological films when the intra-bronchial pressure was raised.

The present paper describes a method of coronary angiography developed at Karolinska Sjukhuset, Stockholm, and applied in 100 cases of ischaemic heart disease. The appearance of short localized stenosis in the proximal part of the coronary arteries, of total blocking of one of the vessels, and of new and old collateral vessels, is described. The diagnostic importance of variations in the speed of filling and emptying of certain vascular areas is stressed. It was possible to demonstrate the site of obstruction of central vessels and the appearances of diffuse coronary atherosclerosis. In 13 cases localized accumulation of contrast material was observed in the left ventricular wall; this may have represented richly vascularized regions in clinically suspected infarcts. Visualization of the coronary veins has not yet proved to be of diagnostic value. *Leon Gillis*

1167. A New Method of Visualization of Atrial Septal Defects during Angiocardiology. (Ein neues Verfahren zum angiokardiographischen Nachweis eines Vorhofseptum-defektes)

H. H. HILGER, P. THURN, A. DÜX, and A. SCHAEDE. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 591-596, May, 1962. 2 figs., 10 refs.

Atrial septal defects present many difficulties in angiocardiology if the shunt is from left to right and, until recently, only selective left angiocardiology has provided

useful information. The authors, working at the Medical Clinic of the University of Bonn, have shown that ordinary right angiocardiology is sufficient if the contrast medium is injected at the peak of the first inspiration after a Valsalva test of 15 seconds' duration. This procedure, by compressing the pulmonary veins, impedes the filling of the left atrium, whereas the right atrium is engorged with blood to which 20 ml. of the contrast agent adds further volume. The result is a reversed shunt which clearly demonstrates the defect.

F. M. Abeles

1168. Aortography with the Aid of the Valsalva Test. (Aortographie unter Valsalva-Bedingungen)

H. LUDIN. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 611-617, May, 1962. 7 figs., 10 refs.

The fact that Valsalva's manoeuvre reduces the speed of the arterial blood flow (partly by reducing the venous blood supply to the heart and partly by increased pressure on the arteries in the chest and abdomen) has been applied by the author, working at the Radiological Institute of the University of Basle, to achieving better contrast density in aortography. The reduced arterial flow enables the whole aorta to be visualized by simple direct retrograde injection from the groin without the aid of a catheter, and better contrast is obtained than by other methods. Since filling is strictly gravitational, it is possible to obtain visualization of all renal vessels without interference from the coeliac or mesenteric arteries, which can be filled only if the patient is prone. Coarctation of the aorta is best visualized by injecting the bronchial artery.

F. M. Abeles

1169. Left-sided Angiocardiology. (Zur Angiokardiographie des linken Herzens)

S. PAULIN. *Fortschritte auf dem Gebiete der Röntgenstrahlen und der Nuklearmedizin* [Fortschr. Röntgenstr.] 96, 618-625, May, 1962. 9 figs., 17 refs.

For assessment of either aortic or mitral incompetence left angiocardiology is indispensable. The author, working at the University of Gothenburg, Sweden, uses a thin-walled Ödman-Ledin catheter allowing 76% "urografin" to be injected at the high speed of 40 ml. per second with the aid of the Gidlund syringe. By means of a copper wire (which is later removed), the distal part of the catheter is shaped into a ring lying at right angles to its long axis. Holes, facing outwards for the aorta and coronary arteries and inwards for the left ventricle, are made in the circular part. This arrangement prevents penetration of contrast agent into the muscle wall, which may lead to extrasystoles.

F. M. Abeles

1170. Angiocardiological Technique in Intracardiac Shunts J. DOW and D. G. TAYLOR. *British Journal of Radiology* [Brit. J. Radiol.] 35, 241-248, April, 1962. 10 figs., 14 refs.

One of the essentials for successful angiocardiology is the selective delivery of an adequate amount of contrast medium into one of the chambers of the heart within a sufficiently short time, usually about one second. This procedure by means of conventional cardiac catheters necessitates the use of very high injection pressures which are potentially dangerous and tend to dislodge the catheter tip from the appropriate cardiac chamber. The authors, writing from Guy's Hospital, London, describe a method of right-

sided angiocardiology in which wide-bore polyethylene tubing is used instead of conventional cardiac catheters. The preparation of the catheter is described. The material is so cheap that each catheter is used only once and then discarded, thus obviating the risk of the serum reactions which are occasionally encountered after the repeated use of cardiac catheters. The method of right atrial and right ventricular angiocardiology, which is described in detail, has been found to be extremely successful in a large number of cases.

Patients with a left-to-right shunt are investigated, first by excluding extracardiac communications by retrograde aortography, and then by attempting to pass the catheter from the aorta into the left ventricle to demonstrate intracardiac shunts. It was found that percutaneous arterial catheterization as described by Seldinger was not satisfactory because it was not possible even with the largest Seldinger tubing to deliver sufficient contrast material quickly enough to demonstrate the anatomy as clearly as was desirable. Accordingly the method of open arteriotomy with the introduction of a polyethylene catheter has been adopted, the right femoral artery being used in the majority of cases. The procedure is carried out by the staff of the radiological department without surgical assistance. In many cases after the aortogram the catheter can be manipulated through the aortic valve and a left ventricular angiocardiology obtained. If difficulty is experienced a Seldinger guide-wire is inserted until its tip passes beyond the end of the polyethylene tubing; usually the guide-wire passes into the left ventricle after three or four attempts. The polyethylene tube is then also advanced; it follows the wire into the ventricle and after the position has been checked the guide-wire is withdrawn. In 18 cases in which the guide-wire was used the ventricle was entered easily.

Arnold Appleby

1171. Percutaneous Transhepatic Cholangiography: a Modified Technique

S. SHALDON, K. M. BARBER, and W. B. YOUNG. *Gastroenterology* [Gastroenterology] 42, 371-379, April, 1962. 5 figs., 14 refs.

It is of surgical importance to distinguish, if possible, between cases of biliary stasis and jaundice due to an intrahepatic cause such as cirrhosis and those following extrahepatic obstruction from stone, neoplasm, or other condition. The authors describe their technique of percutaneous cholangiography, which is based upon the fact that in the latter group of cases the intrahepatic ducts will be dilated and in the former they will not.

A small-bore, thin polyethylene tube is passed over a needle and introduced into the liver by a percutaneous route. The needle is then removed and the tube slowly withdrawn while suction is applied. On obtaining bile an injection of 40% "hypaque" (sodium diatrizoate) is given under screen control and radiographs are taken. The tube can subsequently be left *in situ* if biliary drainage is desired.

At the Royal Free Hospital, London, 30 patients have been examined in this way. Of these, 24 had extrahepatic obstruction and in all of them bile was aspirated; in 22 a successful cholangiogram was obtained. In the remaining 6 cases, which were thought to be due to intrahepatic obstruction, no bile was obtained and laparotomy in 5 cases revealed no extrahepatic obstruction. The use of the polyethylene catheter reduces the risk of trauma to the liver

and of biliary peritonitis, while ability to continue drainage may be valuable.

The cholangiogram not only serves as an aid in the diagnosis of the obstructing agent, but may help the surgeon materially in displaying the available hepatic duct for the purpose of anastomosis or repair.

A. M. Rackow

1172. Percutaneous Transhepatic Cholangiography: Discussion of the Method and Report of 25 Cases

J. A. EVANS, F. GLENN, B. THORBJARNARSON, and Z. MUJAHED. *Radiology* [Radiology] 78, 362-370, March, 1962. 7 figs., 13 refs.

After a brief historical review of methods employed for opacification of the biliary tree, the authors describe the technique of transhepatic cholangiography used at the New York Hospital. The approach is from just below the right costal margin in the mid-clavicular line, a 7-inch (17.7-cm.) 20- or 21-gauge needle being directed towards the opposite nipple. The needle is passed into the liver and bile is aspirated when a dilated duct is encountered. An injection of 10 to 20 ml. of 75% "hypaque" (sodium diatrizoate) is then given and radiographs are taken. Mention is made of the alternative use of a polyethylene catheter over the needle, the latter being withdrawn; this is considered to provide an additional safety factor.

Percutaneous transhepatic cholangiography was carried out in 25 cases, in 19 of which the ducts were successfully injected. All 19 patients had extrahepatic obstruction due to stone or carcinoma or both and all had jaundice. Of the 6 patients, 5 of them jaundiced, in whom the examination was not successful, 2 proved to have intrahepatic and 4 to have extrahepatic obstruction but in one of the latter group the ducts were not dilated while in another this was not determined. Percutaneous transhepatic cholangiography is considered to be of value: (1) in differentiating between obstructive and non-obstructive jaundice; (2) in determining the presence and site of carcinoma of the biliary system; (3) in demonstrating the site and number of calculi in the ducts; (4) in elucidating the status of the biliary tree in cases of congenital biliary atresia; and (5) in investigating certain puzzling cases of the post-cholecystectomy syndrome.

There were complications in 2 of the authors' cases—namely, intraperitoneal haemorrhage in one and leakage of bile in one. Facilities for surgical exploration of the abdomen should be available if needed following the examination.

A. M. Rackow

1173. Parietography of the Stomach

J. FRIMANN-DAHL and K. TRÆTTEBERG. *British Journal of Radiology* [Brit. J. Radiol.] 35, 249-254, April, 1962. 7 figs., 3 refs.

Parietography of the stomach is a method of demonstrating the thickness of the gastric wall, which cannot normally be estimated from routine radiographs. Oxygen is injected into the peritoneal cavity (1,500 to 2,000 ml.) and the patient is then given an effervescent drink; in this way the stomach becomes distended with gas. Tomograms of the stomach are then taken. The authors emphasize the importance of filling the lesser sac of the peritoneum with oxygen, and this is aided by using a tomograph table which can be tilted to bring the patient towards the erect posture.

At Ullevål Hospital, Oslo, 65 patients have been examined by this technique in the last 2 years. Brief descriptions of

some of these are accompanied by illustrations and a report of the findings at operation. The method has proved to be most useful in regions of the stomach other than the pyloric antrum where peristaltic movement may result in equivocal findings. Infiltration may be shown to extend far outside the lumen of the stomach. Useful evidence of neoplastic infiltration has also been obtained in cases of partial gastrectomy.

A. M. Rackow

RADIOTHERAPY

1174. Experience with and Indications for Interstitial Radioactive Gold Grain Implants

D. A. L. DICK and S. R. USISKIN. *Journal of the Canadian Association of Radiologists [J. Canad. Ass. Radiol.]* 13, 14-18, March [received May], 1962. 5 refs.

A technique of implantation of radioactive gold grains in which the Royal Marsden Hospital gun with a 1.43 mm. diameter needle is used is described in this paper from the Cancer Clinic, Edmonton, Alberta. Although dose rate is measured following implantation, the authors consider that calculation from radiographs gives a more accurate estimation of the dose achieved. For most implants seeds of low activity, 3-2 mc., are recommended. Dosage was between 5,500 and 7,000 r. depending on the site and size of the treated volume. Regulations require a patient to be in hospital if more than 30 mc. are used. Conditions suitable for this form of treatment are carcinomata of the lip, skin, soft palate, posterior pharyngeal wall, bladder, posterior third of the tongue (in addition to external radiation), and lesions at the canthus of the eye extending into the orbit. It is also valuable in cases of local recurrence after vulvectomy, large septic fungating masses, inoperable or recurrent involvement of lymph nodes in the neck, and Kaposi's sarcoma.

The authors state that 89 cases have been treated, but the number of patients in each disease group was too small to make statistical evaluation possible.

M. Sutton

1175. The Contribution of Radiology to the Diagnosis and Treatment of Lymph-node Sarcoma. (La part de la radiologie dans le diagnostic et le traitement des sarcomes ganglionnaires)

R. P. DELAHAYE. *Journal de radiologie, d'électrologie et de médecine nucléaire [J. Radiol. Électrol.]* 43, 153-166, March-April, 1962. 20 figs.

This study, from the Val-de-Grâce Hospital, Paris, is based on 47 cases of lymph-node sarcoma verified histologically and on 8 cases of mediastinal tumour not verified histologically but having all the clinical and radiological features of nodular sarcoma. Only sarcomata originating from lymph nodes are considered. Two main types occur, the localized and the generalized, and it is difficult to say whether or not the latter is an extension of the former. In the mediastinal cases the x-ray appearances may be similar to those of Hodgkin's disease. Extension into the pulmonary parenchyma may occur, radiation from the hilar region giving the appearance of a bronchial carcinoma. Non-homogeneous opacities may be seen in the upper part of the lung field, and these might at first sight be taken for pneumonitis. Pulmonary lesions are generally accompanied by extensive lymph-node involvement. Pleurisy with effusion is com-

mon, more so than in the reticulosarcomata. In only 6 cases in the present series did the condition arise in the abdomen, but according to some authors the abdomen is a more common site of origin than the mediastinum. Clinically, any intra-abdominal disease may be simulated, and oedema of the lower limbs and ascites may occur. In some cases the presenting feature is an intra-abdominal mass. Various radiological procedures may aid diagnosis, but the diagnosis of abdominal sarcoma is usually made on exploration. Lymph-node sarcoma most commonly arises in more than one region, in the following order of frequency: cervical and mediastinal, retroperitoneal and inguinal, axillary and mediastinal. Radiotherapy remains the treatment of choice, and the majority of the author's cases were treated by irradiation alone, which may be curative in the localized type. Of 15 patients treated, 4 were alive 5 years later and 2 over 10 years later. In the generalized types treatment can only be palliative.

John H. L. Conway-Hughes

1176. Roentgen Therapy of Primary Gastrointestinal Lymphoma

J. C. COOK and D. P. CORBETT. *Radiology [Radiology]* 78, 562-569, April, 1962. 36 refs.

The authors review 66 cases of lymphoma in which the disease appeared to originate in the gastro-intestinal tract or its mesentery and in which treatment was primarily with x-irradiation. The series represented 6.5% of all the lymphomata, excluding leukaemias, seen at the Harper Hospital, Detroit, between 1922 and 1961. X-ray examination was the chief diagnostic aid used. Laparotomy and biopsy were performed on 43 patients, and partial removal of the tumour in 11. The diagnosis was established in the remaining cases by biopsy examination of distant metastases or at necropsy. The final diagnosis was lymphosarcoma in 45 cases, reticulosarcoma in 14, giant follicular lymphoma in 2, and Hodgkin's disease in 5. In all the cases of Hodgkin's disease the pathological process originated in the mesentery. During the earlier years treatment was by 200 kV. x rays with 1 mm. Cu filtration and half-value layer of 1 mm. Cu. Later, 225 to 250 kV. x rays were used, with Thoraeus filtration and half-value layer 3 mm. Cu. Localized cases (Stage I) were given single exposures of 700 to 800 r. tumour dose to diseased superficial nodes, the abdomen being treated by a single exposure to 4 or 5 fields on successive days to a tumour dose of 1,200 to 1,600 r. Generalized cases (Stage II) received single treatments to each of 10 to 14 fields in as many days. No chemotherapy was given.

The prognosis in reticulum-cell sarcoma was better than in lymphosarcoma, the 5-year survival rates being 44% and 33% respectively. The 5-year absolute survival rate for these 2 groups together was 35.7%, which was higher than the rate for the entire series. The incidence in females was only half that in males, but the prognosis was better. The outlook was best in the age group of 21 to 50 years. The number of cases and the 5-year survival rates for each region of the gastro-intestinal tract are given. The site of origin of lymphosarcoma and its treatment by surgery or x-irradiation is discussed with reference to the literature. Comparison with a series of lymphosarcomata and reticulum-cell sarcomata from other sites, previously reported from the same hospital, suggests that the prognosis of those arising in the gastro-intestinal tract or mesentery is similar to the prognosis of the totality.

M. B. Duthie

ABSTRACTS OF WORLD MEDICINE

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Pathology

1177. Pulmonary Tumours in Mice Induced by Oral Isoniazid and Its Metabolites

C. BIANCIFIORI and R. RIBACCHI. *Nature [Nature (Lond.)]* **194**, 488-489, May 5, 1962. 4 refs.

The development of pulmonary adenomata in mice given isoniazid by intraperitoneal or subcutaneous injection or by mouth has been described by several workers. An investigation was carried out at the University of Perugia to determine the frequency with which tumours develop in mice receiving isoniazid, hydrazine sulphate, and the sodium salt of isonicotinic acid. The drugs were given by mouth in a watery solution each day over a period of 46 weeks, when the mice were killed. In all the animals receiving isoniazid or hydrazine sulphate pulmonary tumours developed, whereas in only 19% of those given the sodium salt of isonicotinic acid did tumours develop. No tumours were seen in 216 control mice observed at the same time. The induced tumours were multiple in all the mice treated with the first two compounds. A large proportion had the structure of papillary or solid adenomata, but 15 tumours were judged on histological grounds to be undergoing malignant change. In addition 10 tumours were regarded as carcinomata on the grounds of atypical structure or local invasion. In one mouse given hydrazine sulphate there were metastases to the liver and ovary. It has been shown that isoniazid is metabolized to isonicotinic acid and hydrazine, and the results here reported suggest that the tumours which develop are the result mainly of the liberation of hydrazine. If this is so, any drug which liberates hydrazine in metabolism must be regarded as potentially carcinogenic and its use in medicine limited.

R. F. Jennison

1178. Cancer Cells in the Peripheral Circulation. (Recherche des cellules cancéreuses dans le sang circulant)

J. FRIDEN-KILL and W. H. MINDER. *Schweizerische medizinische Wochenschrift [Schweiz. med. Wschr.]* **92**, 915-918, July 28, 1962. 2 figs., 35 refs.

The authors, at the Westeinde Hospital, The Hague, used the following method for examining the blood of cancer patients for malignant cells: 10 ml. of blood taken from a cubital vein is mixed with a solution of 620 mg. of bovine fibrinogen in 9 ml. of water and 5 ml. of an isotonic solution of sodium chloride, and stood for 30 minutes to allow the erythrocytes to sediment. The supernatant liquid is spun at 1,500 revolutions per minute for 10 minutes and the deposit spread on slides and stained by the May-Grünwald-Giemsa method. The authors have found this preferable to embedding the deposit in paraffin and cutting sections.

Malignant cells were found in cases of cancer of different sites as follows: lung, 10 of 46 cases; uterine cervix, one of 9; stomach, 4 of 9; colon, one of 2; miscellaneous sites (limbs, pharynx, thyroid, etc.), 9 of 34; breast, 0 of 53;

ovary, 0 of 4. Cancer cells were rarely found in early cases and were present in about 25% of the advanced cases. Their presence was regarded as of some prognostic significance, as 60% of the patients in whom they were found died within a few months of the blood examination, as compared with 30% of those in whom they were not detected. The authors did not find that removal of specimens of cancer of the bronchus or uterine cervix for biopsy tended to liberate tumour cells into the blood stream [but the time relation between removal of tissue for biopsy and removal of blood for examination for cancer cells is not specified.]

M. C. Berenbaum

1179. The Thyroid Cytotoxic Autoantibody

I. J. FORBES, I. M. ROITT, D. DONIACH, and I. L. SOLOMON. *Journal of Clinical Investigation [J. clin. Invest.]* **41**, 996-1006, May, 1962. 2 figs., 24 refs.

The authors, working at the Middlesex Hospital, London, studied the ability of various sera to kill freshly cultured human thyroid cells during incubation for 18 to 24 hours. The cytotoxic effect of serum required complement and was removed by heating the serum at 56° C. The antibody behaved on electrophoresis, chromatography, and ultracentrifugation like a γ -globulin of low molecular weight (7 Svedberg). There was no consistent relationship between the presence of cytotoxic antibody and the antibody to thyroglobulin, and absorption studies suggested that the cytotoxic antibody was directed against the microsomal thyroid antigen and not thyroglobulin. There was, however, a close relationship between cytotoxicity and the presence of complement-fixing antibodies to thyroid microsomes and cytoplasmic-staining antibody. Experiments with cells dispersed with ficin suggested that trypsinization increased the sensitivity of the cells to the antibody. Thyroid cells lost their sensitivity to death from cytotoxic antibody with increasing time of culture *in vitro*. This was correlated with loss of staining by the cytoplasmic antigen and was probably due to loss of organ-specific microsomal antigen. Cells with a high content of microsomal antigen were in general most readily killed.

Clinically, the antibody occurred in 46 out of 48 patients with Hashimoto's thyroiditis, all 6 patients with focal thyroiditis, 6 out of 9 patients with myxoedema, and 34 out of 51 with thyrotoxicosis, but in only 5 out of 31 patients with non-toxic nodular goitre. The incidence in relatives of 54 patients with thyroid disease was 34 out of 118 (29%) and in controls 8 out of 91 (9%). Cytotoxic antibody occurred in one out of 15 mothers of cretins.

The authors conclude that the cytotoxic factor is a γ -globulin antibody of low molecular weight, able to kill the patient's own thyroid cells in tissue culture in the presence of complement and involving the same antibody-antigen

system as the complement-fixing antibody to microsomes and the cytoplasmic staining (immunofluorescent) antibody. Damage to the cell surfaces was probably required to allow cytolysis, and the occurrence of cytotoxic antibody in thyrotoxicosis suggested that the antibody did not necessarily cause tissue damage. It is postulated that the antibody may, however, act synergically with lymphocytes, which are believed to enter thyroid cells. *G. L. Asherson*

1180. The Autoimmune Response in Myasthenia Gravis
R. G. WHITE and A. H. E. MARSHALL. *Lancet [Lancet]* 2, 120-123, July 21, 1962. 3 figs., 20 refs.

Changes in the thymus gland have been noted in 60% of patients with myasthenia gravis. That these changes may be due to an autoimmune response by the thymus led the authors, at the London Hospital, to investigate 16 patients with active myasthenia gravis.

The serum of 6 of the patients was positive when tested for antinuclear factor. This test is performed by adding the patient's serum to frozen sections of normal thyroid tissue. The sections are then exposed to fluorescein-conjugated rabbit anti-human γ -globulin. A bright fluorescence of the thyroid-cell nuclei is observed microscopically, and indicates a positive result. This phenomenon does not occur with control sera. Frozen sections were also made of 6 thymus glands obtained at thymectomy from patients with myasthenia. When these sections were treated with fluorescein-conjugated rabbit anti-human γ -globulin, the germinal cells, which are a feature of the myasthenic thymus, showed fluorescence. This indicated that these cells were producing γ -globulin. A striking finding was the bright fluorescence of certain of the Hassall's corpuscles. In the normal thymus some fluorescence is seen in the region of the penetrating vessels of the gland capsule, but in myasthenia fluorescence is noted well within the gland. The occurrence of antinuclear factor and γ -globulin producing cells in the gland is evidence that autoimmunity is a feature of this condition. Taken together with previously observed associations, such as acute haemolytic anaemia and thymus tumours, and the development of myasthenia gravis in lupus erythematosus and rheumatoid arthritis, it strengthens the view that a relationship exists between these conditions. *J. S. Malpas*

1181. Gastro-intestinal-specific Antigen: an Immunohistological and Serological Study

R. C. NAIRN, J. E. FOTHERGILL, M. G. MCENTEGART, and I. B. PORTEOUS. *British Medical Journal [Brit. med. J.]* 1, 1788-1790, June 30, 1962. 1 fig., 6 refs.

The authors, working at the University of Aberdeen, studied the distribution of an antigen present in human gut mucosa by the complement-fixation, gel diffusion, and immunofluorescent techniques. Antisera against the microsomal fraction of human colon were prepared in rabbits. Absorption studies demonstrated antibody against antigen specific to human gut by the complement-fixation technique. Microsome material from colon carcinoma lacked one of the antigens with which the sera reacted. Thus, although the activity of the sera could be entirely absorbed by normal colon microsomes, it was only partly absorbed by microsomes from malignant colon. In contrast, the antibody demonstrated by gel diffusion could be absorbed by normal and malignant colon microsomes. The antisera stained the

gastro-intestinal mucosa brightly in the immunofluorescent test and this staining was removed by absorption with colon mucosa microsomes but not by malignant colon microsomes. Microsomes were more effective after ageing, presumably because a soluble antigen was released.

The staining involved some of the mucosal glands of the gastro-intestinal tract, including the superficial cells of the stomach, the goblet cells of the small intestine, and all the epithelial cells of the colon. All the areas which stained gave positive reactions for acid mucopolysaccharides, but the converse was not true. Some of the mucosal secretions of the bowel stained, but glandular tissue outside the gastro-intestinal tract did not stain. Specific staining of the small intestine was seen in early foetal tissue.

The authors conclude that they were dealing with a gastro-intestinal specific antigen which was probably an acid mucopolysaccharide. *G. L. Asherson*

1182. Loss of Gastro-intestinal-specific Antigen in Neoplasia
R. C. NAIRN, J. E. FOTHERGILL, M. G. MCENTEGART, and H. G. RICHMOND. *British Medical Journal [Brit. med. J.]* 1, 1791-1793, June 30, 1962. 3 figs., 17 refs.

In the previous paper (see Abstract 1181) the authors provided evidence by absorption studies that sera prepared against human colon mucosa contained an antigen, specific to the gastro-intestinal tract, which can be absorbed out by colon mucosa microsomes but not by microsomes from malignant tumours of the colon. They now report the results of staining neoplasms of the colon by these sera by means of the immunofluorescent technique.

Of 54 carcinomata of the colon, 45 showed no staining although the adjacent normal colon stained. Some adenocarcinomata contained a few brightly staining cells, and occasionally staining of mucin was seen in mucoid carcinomata. One gastric and 3 colonic polyps which were considered to be pre-malignant showed fluorescence of the neoplastic pattern, although more cells stained. The staining of 8 benign colonic polyps, including one from a patient with the Peutz-Jeghers syndrome, resembled that of normal mucosa. These findings, the authors state, provided another example of loss of organ-specific antigen in malignancy. They suggest that the loss of antigen may be due to loss of a gene, failure of a gene to make its presence manifest (incomplete penetrance), or loss of a particulate cytoplasmic factor required for mucin production. They wonder whether loss of antigen *per se* favours metastasis, perhaps by altering cell adhesion. *G. L. Asherson*

1183. An Attempt to Desensitize Guinea-pigs Sensitized to Egg-white. (Essai d'un traitement désensibilisant chez des cobayes sensibilisés au blanc d'œuf)
E. MUSSO and R. BRUN. *Acta allergologica [Acta allerg (Kbh.)]* 17, 105-111, 1962. 2 refs.

Guinea-pigs were sensitized to egg-white by a single subcutaneous injection of 0.5 ml. of a 1 in 10 dilution. An attempt was made 21 days later to desensitize the animals by multiple injections of egg-white, starting with 0.1 ml. diluted to 1 in 10⁶ and reaching a dilution of 1 in 10 after 100 to 114 days. The guinea-pigs were not desensitized; in fact skin reactions to the egg-white were more intense than in control animals. This finding is in contrast to that in guinea-pig eczematously sensitized to dinitrochlorobenzene.

A. W. Frankland

Microbiology and Parasitology

1184. Sterile Syringes for the General Practitioner
D. STARK MURRAY. *Lancet* [*Lancet*] 1, 1343-1344, June 23, 1962.

In a previous paper (*Lancet*, 1954, 1, 1274) the author described a method of packing syringes for sterilization and transport. It is based on the use of an aluminium container holding five 2-ml., four 5-ml., and two 10-ml. syringes and one 20-ml. syringe. As a result of experience gained since then he considers that this method of packaging syringes has much to recommend it and that in spite of the frequency with which the box must be opened before the supply of syringes is exhausted they remain sterile. He therefore considers that the packing of syringes each in its own container as recommended in a recent memorandum from the Medical Research Council is not warranted, being no safer and more expensive than the method described. *R. Hare*

1185. *Histoplasma capsulatum* and House Bats in Trinidad
C. W. EMMONS and A. M. GREENHALL. *Sabouraudia* [*Sabouraudia*] 2, 18-22, June, 1962. 1 fig., 11 refs.

Saprophytic growth of *Histoplasma capsulatum* in soil enriched by the droppings of bats has been observed in two areas in the U.S.A. The authors of this paper describe similar observations in Trinidad. Samples were taken of soil lying under the points of ingress and egress of bats in bat-infested premises. Out of 176 samples examined *Histoplasma capsulatum* was isolated from 8; 4 of these were associated with the presence of bats in buildings, 3 having been taken from beneath a bat roost above the buttressed roots of a silk-cotton tree and one in a small abandoned ammunition dump inhabited by bats. These findings are considered to indicate a wider distribution of *H. capsulatum* in Trinidad and a greater frequency of human exposure than earlier information indicated. *R. R. Willcox*

1186. Studies in "Hospital Strains" of *Staphylococcus aureus* Isolated from the Naso-pharynx of Hospital Personnel. With Special Reference to Their Difference in Different Wards and in Different Occupation Groups. [In English]
O. WIDHOLM and R. MÄKITALO. *Annales chirurgiae et gynaecologiae Fenniae* [*Ann. Chir. Gynaec. Fenn.*] 51, 179-188, 1962. 9 refs.

The authors have studied the carrier rate of *Staphylococcus aureus* among the nursing staff of different wards of Helsinki University Central Hospital, Finland. Nose and throat swabs were taken from 450 members of the staff, plated on blood agar plates, and then transferred to tubes of broth. Both plates and tubes were incubated for 24 hours at 37° C. The presence of *Staph. aureus* was established by subculture and the result of the coagulase test. The strains were phage-typed and tested for sensitivity to antibiotics.

Of the 450 members of the staff 196 (44%) were found to be carriers of *Staph. aureus*. In the gynaecological wards 48% were carriers, in the obstetric wards 44%, and in the "mixed" wards 35%. The carrier rate was highest in children's nurses and trainees; in medical students it was 51%, in doctors 45%, in ward helps 44%, assistant nurses 43%, and nurses 41%. The rate was lowest in midwives (29%).

The authors point out that the carrier rate among children's nurses reflected "the staphylococcal incidence of virtually the obstetric wards alone, while doctors, medical students, and midwives are also attached to the obstetric wards".

In the gynaecological wards 60% of the staphylococcal strains were resistant to penicillin, streptomycin, and tetracycline, but in the obstetric wards the percentage was 15 and in the mixed wards 10. No less than 30% of all strains were resistant to antibiotics. The resistant staphylococcal strains predominating in the gynaecological wards were phage groups I and III, mainly types 52/52A/80 and 53. In the obstetric wards a wider variation of phage types was found and these strains were predominantly antibiotic-sensitive.

The authors consider that their findings in the gynaecological wards can be explained on the basis of the longer stay in hospital of the patients, surgical treatment, and antibiotic therapy "prescribed more readily" than in the obstetric wards, which favours the emergence of "hospital strains" of resistant staphylococci. In the obstetric and mixed wards the stay is shorter and antibiotics are used less often, so that there are a wider range of phage types and more sensitive organisms. *A. E. Wright*

1187. On the Toxicity of the "Toxoid" Preparation Responsible for the Kyoto Catastrophe in 1948
M. KUROKAWA and R. MURATA. *Japanese Journal of Medical Science and Biology* [*Jap. J. med. Sci. Biol.*] 14, 249-256, Dec., 1961 [received June, 1962]. 1 fig., 7 refs.

On November 4 and 5, 1948, in Kyoto, Japan, 15,561 infants and children received a second dose of a preparation of alum-precipitated diphtheria toxoid. Of this number, 606 infants and children became ill one to 2 days after immunization, with oedema, vesiculation, and necrosis at the inoculation site; 68 died, 9 with signs of acute diphtheritic paralysis. The manufacturers had carried out the detoxication process of the batch of alum-precipitated toxoid (A.P.T.) in four different bottles and had filled the final vials directly from these bottles without performing toxicity tests or pooling the contents. Failure to pool the contents explained the occurrence of accidents in some clinics and not in others, although the same batch of A.P.T. had been used. Investigation of the remaining, serially numbered, vials confirmed this uneven distribution of toxic contents and showed that it was contents with a pH of 6.6 to 7.0 that were toxic. Quantitative titrations by the authors revealed further that the toxin content per ml. was about one-fifth of the minimal lethal dose (M.L.D.) for guinea-pigs. This result differs substantially from that of Barksdale, who, in material from the same catastrophe, found an equivalent of 10 to 20 guinea-pig M.L.D. per ml. When in 1923 at Baden, in Austria, toxin-antitoxin mixtures produced a similar, although smaller, disaster, injection of about 10 M.L.D. for guinea-pigs resulted in the death of 6 of 11 infants. The authors suggest that doses 50 to 100 times smaller can cause severe and fatal reactions in about 10% of infants and children injected with diphtheria prophylactics containing diphtheria toxin. *K. Zinnemann*

Pharmacology and Therapeutics

1188. **Thalidomide and Malformations in Liverpool**
R. W. SMITH. *Lancet [Lancet]* 1, 1270-1273, June 16, 1962. 1 fig., 17 refs.

This study from the University of Liverpool concerns three groups of malformed infants (30 with ectromelia, 7 with microtia, and 22 with lesser limb deficiencies) and a group of 40 normal infants born in 1960 and 1961. Information about thalidomide and other drugs prescribed during pregnancy was obtained in respect of the malformed children from the general practitioner in charge of each case. If it was not certain from the reply that a mother had taken thalidomide during the first trimester, she was visited and questioned. Inquiry was also made about possible virus infections during the first trimester. Of the 30 infants with ectromelia, 19 were male, 11 female; 11 were stillborn or died in the neonatal period. All 4 limbs were involved in 13 cases (43%). Thalidomide had been taken in the first trimester of pregnancy by 12 of the mothers (40%). Virus infections had occurred at 2 to 3 months in 7 (influenza in 6, encephalitis in one). The mothers of 3 of the 7 infants with microtia had taken thalidomide; none had had a virus infection. The mothers of 2 of the 22 infants with lesser limb deficiencies had taken thalidomide and one had had a virus infection. No control mothers had taken thalidomide, but 15 had taken other drugs. The incidence of virus infection in the control group was unknown. The author is firmly of the opinion that thalidomide, and not virus infections or other drugs, is responsible for the deformities; such malformations were very rare in Liverpool before 1959.

I. M. Librach

1189. **Congenital Abnormalities after Thalidomide Treatment.** (Die Thalidomid-Embryopathie).
W. LENZ and K. KNAPP. *Deutsche medizinische Wochenschrift [Dtsch. med. Wschr.]* 87, 1232-1242, June 15, 1962. 6 figs., 13 refs.

The 332 cases of congenital abnormality reported in this study from the University of Hamburg were divided into 2 groups. The first group contained 129 cases seen by the authors at the University Paediatric Clinic or at other clinics in the town and district. These 129 cases were subdivided into 90 in which there was reliable evidence that the mothers had taken thalidomide, 22 in which there was no such evidence, and 17 in which the evidence was doubtful. The second group contained 203 cases brought to the authors' notice, chiefly by letter, because the mothers had taken thalidomide; most of these were in Western Germany, but others were in Belgium, Brazil, Egypt, Great Britain, Israel, Sweden, Switzerland, and the U.S.A.

The most frequent deformity was absence of arms, which was noted in 54.5% of the 90, 54.6% of the 22, 50.0% of the 17, and 50.6% of the 203. A table gives the corresponding figures for other deformities, such as absence of both arms and legs, absence of arms, legs, and ears, of arms and ears, of ears alone, of legs alone, and of other organs. Other anomalies found included spastic hypertrophy of the pylorus, duodenal stenosis, duodenal atresia, congenital heart

disease (34 cases in the total series of 332), anophthalmia or microphthalmia, and anal atresia. As evidence of the increased incidence of phocomelia in West Germany, figures are cited from the University Orthopaedic Clinic at Münster, where one case was seen in 1948 and 65 cases in 1961.

The authors consider that the critical phase during which administration of thalidomide is most likely to lead to embryopathy is from the 37th to the 50th days after the beginning of the last menstrual period. Since November, 1961, they have learned of 139 mothers who were known to have taken thalidomide without any effect on the foetus. Of these, 105 took the drug after the critical phase—that is, after the 50th day. In the authors' view the risk of foetal deformity following administration of thalidomide in the critical phase is over 20%. They conclude that thalidomide is responsible for the increase in phocomelia, and discuss fully their reasons for reaching this conclusion. They consider that, in their 22 cases in which there was no clear history of thalidomide having been taken, the memory of the mothers or of their medical attendants must have been at fault, and that the deformities were unlikely to have been caused by factors other than thalidomide.

[A useful paper summarizing West German experience of thalidomide.]

I. M. Librach

1190. **Damage to the Embryo Due to Thalidomide. Incidence in Germany and Other Countries.** (Thalidomid-Embryopathie. I. Vorkommen inner- und ausserhalb Deutschlands)

H. WEICKER and H. HUNGERLAND. *Deutsche medizinische Wochenschrift [Dtsch. med. Wschr.]* 87, 992-1002, May 11, 1962. 25 refs.

An increase in the incidence of phocomelia in the Rhine-Ruhr area in the early part of 1961 led to this study from the University of Bonn. In the Bonn district during 1960 and 1961 there were 32 cases of phocomelia in 9,000 births (3.56%). From this it is calculated that in the whole of West Germany in the same period children born with phocomelia or phocomelia-like deformity numbered between 4,500 and 6,500, and that two-thirds of these children are alive. Inquiries throughout West Germany and Berlin showed that, where statistics were available, no cases of phocomelia had been recorded for the period 1911 to 1958. According to one set of statistics, in 474,950 births in Berlin between 1911 and 1950 there were 75 (0.16%) cases of polydactyly and 205 (0.43%) of other deformities of the extremities. According to another authority, in 201,692 births in Berlin and its environs between 1950 and 1956, there were 94 cases (0.46%) of polydactyly or syndactyly and 85 (0.42%) of other deformities of the extremities.

Between 1949 and 1956, of 301,937 infants born in the Münster area of Germany 60 (0.2%) had various dysplasias of the extremities; of these, only 3 had true phocomelia, 2 had amelia, and 29 had hypoplasia or aplasia of the long bones. Inquiries regarding the incidence of phocomelia in the early part of 1961 were also made in Austria, Canada, East Berlin, France, Great Britain, Hungary, Italy, the

Netherlands, the Philippines, Poland, Portugal, Spain, Switzerland, and the U.S.A. The results showed that in some 500,000 births there were 15 cases (0.03%) of true phocomelia and 35 (0.07%) of phocomelia and amelia. A high incidence was reported from the Liverpool-Boothle area in England, where the 36,000 births of 1960 and 1961 included 29 cases of phocomelia (0.778%). On the basis of these figures from Liverpool, the authors calculate that some 1,400 cases of phocomelia and phocomelia-like deformities must have occurred throughout Great Britain. They are confident that this high incidence in Great Britain and West Germany is due almost entirely to the administration of thalidomide during the first 8 weeks of pregnancy.

I. M. Librach

1191. **The Increased Incidence of Congenital Malformations of the Limbs and their Possible Aetiology.** (Beitrag zur Häufung von kongenitalen Missbildungen der Gliedmassen und ihre mögliche Ätiologie)

H. WEGERLE. *Medizinische Klinik [Med. Klin.]* 57, 877-883, May 18, 1962. 6 figs., bibliography.

At the University Orthopaedic Clinic, Marburg, Germany, between January, 1960, and January, 1962, the author saw 23 cases of congenital defect of the extremities, 14 of dysplasia of the radius, 6 of brachial phocomelia, 2 of finger defects, and one of hypoplasia of the femur. No cases of this type had been seen between 1954 and 1959, this local increase corresponding with the present increase throughout Western Germany. Of 20 mothers of children with radial defects and phocomelia, 13 gave a history of having taken thalidomide in the first 3 months of pregnancy, but no such history was elicited from the mothers of children with finger defects only. The author concludes that a dosage of 100 to 200 mg. of thalidomide is teratogenic. The mothers of 60 healthy infants born between 1960 and 1961 were also interviewed, but only one gave a history of having taken thalidomide during the first 2 months of pregnancy. The author also considers other possible aetiological factors—genetic, chemical, toxic, and virus infections. He considers that his results are strongly in favour of thalidomide being the causal agent, but that further study will be necessary to establish an absolute connexion.

I. M. Librach

1192. **α -Methyl-dopa: Therapeutic Trials in Hypertension and Biochemical Investigation of Its Mode of Action.** (α -Methyl-Dopa: Therapeutische Erfahrungen bei Hypertonie und biochemische Untersuchungen zu seiner Wirkungsweise) F. SCHAUB, F. NAGER, H. SCHAER, W. ZIEGLER, and P. LICHTLEN. *Schweizerische medizinische Wochenschrift [Schweiz. med. Wschr.]* 92, 620-628, May 19, 1962. 6 figs., 25 refs.

At the University of Zurich α -methyl-dopa (α -methyl-3,4-dihydroxy-L-phenylalanine; "aldomet"), which is a competitive inhibitor of the decarboxylation of dihydroxyphenylalanine (dopa) to dihydroxyphenethylamine (dopamine), and thus interferes with the synthesis of noradrenaline, was tried in 44 patients with hypertension and in 7 normotensive controls, and its effect on the blood pressure statistically evaluated. When the drug was administered orally to 23 in-patients, in a dosage initially of 0.5 to 1.5 g., followed by a daily maintenance dosage varying between 0.5 and 4.0 g. (average 1.5 g.), for periods ranging from 6 to 90 days, the average fall in blood pressure was 40 mm. Hg (21%) systolic

and 18 mm. Hg (15.5%) diastolic in the erect position and 29 mm. Hg (15%) systolic and 13 mm. Hg (10%) diastolic in the supine position. In ambulant patients, whether previously stabilized as in-patients or treated solely as out-patients, combination of this compound with diuretics and guanethidine was necessary to achieve a persistent reduction in blood pressure. Side-effects included somnolence, which disappeared after 3 to 4 days either spontaneously or after reduction of the dose, giddiness, and diarrhoea. Orthostatic symptoms were observed in only 2 patients. The fall in blood pressure after intravenous injection of doses varying between 0.25 and 1.75 g. in 11 hypertensive patients was about twice that in 6 normotensive controls; somnolence occurred in all these cases. A reduction in the urinary excretion of 3-methoxy-4-hydroxymandelic acid, which was statistically significant but which was not proportional to the reduction in blood pressure, followed treatment with α -methyl-dopa in 12 hypertensive subjects with normal excretion of catechol amines. This observation, and others discussed in some detail, suggest that the mode of action of α -methyl-dopa is more complex than the inhibition of decarboxylation of dopa. It is concluded that α -methyl-dopa is an effective and well-tolerated hypotensive drug, particularly when given in combination with small doses of other hypotensive compounds, but that further observations are necessary to establish its value in the treatment of hypertension.

A. Schott

1193. **Tranquillizers, Barbiturates, and the Brain**

H. E. HIMWICH. *Journal of Neuropsychiatry [J. Neuro-psychiat.]* 3, 279-294, June, 1962. 18 figs., 19 refs.

The basic actions of different psychotropic drugs on key areas of the brain are discussed in this paper from Galesburg State Research Hospital, Illinois. The drugs studied were the phenothiazines, the *Rauwolfia* alkaloids, the meprobamate-like drugs, and the barbiturates, with reference primarily to the areas of the brain that are most sensitive to them. The important areas—the thalamus, reticular formation, limbic system, neocortex, hypothalamus—are all discussed and their various responses to drugs described. For example, the phenothiazines depress the sympathetic function of the hypothalamus, while reserpine stimulates the parasympathetic actions. The barbiturates exert an over-all depressive influence, while meprobamate has no effect on the hypothalamus. Two neurohormones, serotonin and noradrenaline, are blocked by the phenothiazine group of drugs, while reserpine depletes the neurohormonal depots. Meprobamate and barbiturates do not affect these hormones.

The author concludes that the various tranquillizers differ markedly in their effects on key brain areas, and thus in their therapeutic effects in human beings. Further, that tranquillizers, while they have certain similarities in action to the barbiturates, all show marked differences from the latter.

[This is an important paper.]

B. M. Davies

1194. **Survival of Offspring of Rats Administered Phenothiazines During Pregnancy**

O. D. MURPHREE, B. L. MONROE, and L. D. SEAGER. *Journal of Neuropsychiatry [J. Neuro-psychiat.]* 3, 295-297, June, 1962. 1 fig., 6 refs.

The finding that drugs given in early pregnancy can cause malformations of the embryo has given rise to concern about the safety of many of the pharmacological agents now

widely used. A controlled study of the effect of administration of the phenothiazines—chlorpromazine, promazine, and thioridazine—to rats in early pregnancy is described in this paper from the University of Arkansas Medical Center, Little Rock. The drugs were given subcutaneously in a dosage, chosen arbitrarily, of 5 mg. per kg. body weight daily during 18 days of pregnancy. There was a significantly higher mortality among the offspring of the drug-treated animals than among those of the controls. Further, there appeared to be a rise in mortality at the third day. No malformations were noted.

The authors state that no conclusions can be drawn concerning the effect of these drugs in pregnancy in human beings and that long-term studies in this field are desirable.

B. M. Davies

1195. Further Studies of the Effects of Psychotropic Drugs on the Behaviour of Guinea Pigs and Rats

W. T. LIBERSON, P. ELLEN, E. SCHWARTZ, A. WILSON, and V. P. GAGNON. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 298–303, June, 1962. 8 figs., 7 refs.

The effect of some commonly used psychiatric treatment regimens on certain types of behaviour in rats was studied at the Veterans Administration Hospital, Hines, Illinois. [The results are described in detail with illustrations; but only the general implications will be given here. These and similar studies are important in defining the basis for the empirical treatment found effective in clinical psychiatry.]

Tranquillizers pacify certain negative aspects of behaviour without disrupting its integrity. The monoamine oxidase inhibitors—for example, iproniazid—activate certain aspects of behaviour particularly in the direction of positive motivation. Lysergic acid diethylamide breaks down behaviour without sedation and without inducing a state of unconsciousness. Phenobarbitone pacifies animal behaviour, while electric convulsion therapy “at first completely disrupts behaviour”.

B. M. Davies

1196. Pigmentary Retinopathy and Iridocycloplegia in Psychiatric Patients

J. REBOTON JR., R. D. WEEKLY, N. D. BYLENGA, and R. H. MAY. *Journal of Neuropsychiatry* [*J. Neuropsychiat.*] 3, 311–316, June, 1962. 25 refs.

The ophthalmological complications, if any, of the phenothiazine group of drugs were studied in 542 chronic psychiatric patients (all females) at the Cleveland State Hospital and Hawthornden State Hospital, Ohio. The authors describe the course of pigmentary retinopathy, which has been observed by some workers in psychiatric patients receiving these drugs. There is first a subjective complaint of decreased vision in dim light, associated with sluggish pupillary reactions to light. With further impairment of vision fine pigmentation is seen on the retina. Photophobia has occasionally been observed and is perhaps due to sluggish pupillary reactions which also can produce an “inability to focus”. This, the authors consider, is best termed “iridoplegia with or without cycloplegia”; it may be the result of a local accumulation of phenothiazine within the uveal tract.

From their investigation the authors found that these complications were, in fact, rare, in spite of a high daily and total dosage of different phenothiazines. Only one patient had a pigmentary retinopathy which might have been

associated with drug administration. Blurred vision was a common complaint. Objective evidence of iridoplegia was found in fewer than 1% of the patients.

It is emphasized that although the ocular side-effects of psychotropic drugs are uncommon they can be serious.

B. M. Davies

1197. Comparative Analgesic Potency of Heroin and Morphine in Postoperative Patients

C. W. REICHEL, G. M. SMITH, J. S. GRAVENSTEIN, S. G. MACRIS, and H. K. BEECHER. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol. exp. Ther.*] 136, 43–46, April, 1962. 1 fig., 3 refs.

At the Massachusetts General Hospital, Boston, the relief of postoperative pain achieved with morphine in a dosage of 10 mg. per 70 kg. body weight was compared, in a double-blind trial, with the relief given by four different dosages of heroin (1 mg., 2 mg., 4 mg., and 6 mg. per 70 kg. body weight).

All the 522 patients included in the trial had incisional pain due to major thoracic, abdominal, or orthopaedic surgery. Each patient received morphine and one of the dosages of heroin, and in the analysis the mean effect of all the doses of morphine was compared with that of each dose of heroin. The results in patients with moderate, severe, or very severe pain were analysed separately.

It was found that no single dosage of heroin gave equivalent analgesia to 10 mg. of morphine per 70 kg.; there was one value 45 minutes after injection, a higher one at 90 minutes, and a still higher one 150 minutes after injection. The equipotent dosage of heroin ranged from 2.3 to 5.7 (median 4) mg. per 70 kg. A further finding was that 1 mg. and 2 mg. of heroin per kg. were inadequate to relieve very severe postoperative pain. The differences between experimental and pathological pain studies are discussed.

Mark Swerdlow

1198. Subjective Effects of Heroin and Morphine in Normal Subjects

G. M. SMITH and H. K. BEECHER. *Journal of Pharmacology and Experimental Therapeutics* [*J. Pharmacol. exp. Ther.*] 136, 47–52, April, 1962. 1 fig., 11 refs.

A comparative study of the subjective effects of heroin and of morphine in 24 healthy males who were not addicted to the drugs is reported in this paper from Massachusetts General Hospital, Boston. Morphine in a dosage of 10 mg. per 70 kg. body weight, heroin in a dosage of 4 mg. per 70 kg., and a placebo were given serially by subcutaneous injection, there being an interval of at least a week between each injection. The injections were given “so that each of the six ways of ordering the three medications was used with 4 subjects”, a double-blind method being employed. A 90-item list of subjective states was completed at 30 minutes, and 2, 3, and 4 hours after each injection.

The effects of the opiates were most clear-cut in relation to mental clouding, physical activity, and somatic responses (dizziness, itching, numbness, and nausea); the influence of the drugs on emotion was less marked. It was also found that compared with morphine the effects of heroin were stronger and the peak action occurred earlier. With heroin there was some improvement in mood between the second and third hours after injection, whereas with morphine a deterioration of mood occurred during this period.

Mark Swerdlow

Infectious Diseases

1199. **Infectious Diseases as Occupational Risks in Sanatoria and Nursing Homes.** (Infektionskrankheiten als Berufsgefährdung für Personen in Heil- und Pflegeanstalten) B. HENZE. *Zentralblatt für Arbeitsmedizin und Arbeitsschutz [Zbl. Arbeitsmed.]* 12, 134-138, June, 1962. 1 fig.

In the western sector of Berlin, with a population of 2.2 millions and 30,000 hospital beds, there were 1,136 cases of occupationally contracted infectious disease among the entire hospital staff during the 15-year period 1944-58. Of these, 93% were affected with tuberculosis, infective hepatitis, salmonellosis, diphtheria, scarlet fever, shigellosis, and throat infections, and the remaining 7% with 40 other diseases. The predominant disease was tuberculosis, which affected 692 employees. The author discusses these infections and their relation to the different categories of hospital staff. He remarks that, although preventive measures, such as vaccination, for combating infectious diseases can be made compulsory in time of emergency, present opinion in Germany holds that in normal conditions they should only be "recommended", anything else being an infringement of the liberty of the individual. He suggests repeated bacteriological investigation of both nursing staff and newly admitted patients to exclude salmonella or diphtheria infection.

Franz Heimann

1200. **The Nature of Sarcoidosis and Its Relationship to Tuberculosis.** (Das Wesen der Sarkoidose und ihr Verhältnis zur Tuberkulose)

O. KRAUS. *Wiener Zeitschrift für innere Medizin und ihre Grenzgebiete [Wien. Z. inn. Med.]* 43, 169-175, April [received July], 1962. 2 figs., 38 refs.

The author describes 3 cases of sarcoidosis. In 2 of the patients, a 32-year-old married woman and a 45-year-old man, reticulation and enlarged hilar lymph nodes were seen in radiographs of the chest. Examination of lymph-node biopsy specimens showed the typical appearances of sarcoidosis. *Mycobacterium tuberculosis* was not found in the sputum and the Mantoux reaction was negative. In the third case, that of a 20-year-old man, the radiological findings were similar; lymph-node biopsy revealed the presence of sarcoid disease and *Myc. tuberculosis* was present in the sputum.

The author discusses the aetiology of sarcoidosis in the light of published work. He considers that sarcoidosis may be the outcome of a mutation in *Myc. tuberculosis* which prevents it from causing caseation and which might well produce a true causal variant rather than a saprophyte.

I. M. Librach

1201. **Observations on Sarcoidosis.** (Beobachtungen zum Morbus Boeck)

O. ÖGER. *Beiträge zur Klinik der Tuberkulose und spezifischen Tuberkulose-Forschung [Beitr. Klin. Tuberk.]* 125, 241-259, 1962. 4 figs., bibliography.

In a recent German survey, out of a population of 23.5 millions, 1,250 individuals (0.53 per 10,000) were found to have sarcoidosis. Although there is at present no general

agreement as to a specific aetiological agent in this disease, it closely resembles tuberculosis in certain features. Clinically, there are usually surprisingly few symptoms. In this paper are described 64 cases in patients aged between 25 and 53 years. In 45 cases the disease was discovered through mass radiography, and in the remaining 19 in the course of investigation for other complaints. The x-ray appearances varied; bilateral enlargement of hilar lymph nodes, pulmonary infiltration extending from the hila in reticular or strand-like formation, and extensive fibrosis with atelectasis and emphysema, all were seen. Histologically, the lesions consisted of epithelioid-cell tubercles with little or no necrosis. Healing took place primarily by fibrosis, with subsequent formation of a dense scar as the fibrous tissue became compact and hyalinized. In 2 patients small nodules developed in the skin, one patient had lupus pernio, and 3 had osteitis cystica multiplex. In 11 cases the eosinophil granulocytes of the blood were increased from 4 to 9%. In uncomplicated cases the erythrocyte sedimentation rate was normal or slightly raised. In the active proliferative stages, sarcoidosis responded well to cortisone in combination with isoniazid and streptomycin. Of the 64 patients, 62 were kept under observation; in 11 the disease continued to advance, in 13 it remained unchanged, in 11 it improved, and in 27 it was cured.

Franz Heimann

1202. **Sarcoidosis Among Children: a Review**

E. L. KENDIG JR. *Journal of Pediatrics [J. Pediat.]* 61, 269-278, Aug., 1962. 3 figs., bibliography.

VIRUS DISEASES

1203. **Acute Cerebellar Ataxia in Children Associated with Infection by Poliovirus I**

D. MÉNDEZ-CASHION, L. P. SÁNCHEZ-LONGO, M. VALCÁRCEL, and L. ROSEN. *Pediatrics [Pediatrics]* 29, 808-815, May, 1962. 16 refs.

This paper from the University of Puerto Rico and the National Institutes of Health, Bethesda, Maryland, describes 11 cases of acute cerebellar ataxia which occurred among 39 children admitted to an isolation ward with symptoms of disorder of the central nervous system during an epidemic of poliomyelitis. Poliomyelitis virus Type I was found in the faeces of 6 of the 11 children, and in 3 of the 6 there was a marked increase in complement-fixation titre. Neutralizing antibody was absent from convalescent serum specimens of 2 of the children; in one of these the ataxia was probably due to high doses of diphenylhydantoin, while in the other it could be accounted for by the presence of bilateral otitis media.

There was little evidence of spinal involvement, although a few of the children had transient Babinski's sign. A notable feature was facial paralysis, which occurred in 7 cases, and was still present in 3 over a year later. Neck rigidity lasting up to 10 days occurred in 5. In all the cases the ataxia had disappeared within a month. One case is reported in detail. In it the cerebrospinal fluid contained

17 polymorphonuclear leucocytes and 100 lymphocytes per c.mm., and 58 mg. of protein and 67.5 mg. of sugar per 100 ml.

The findings suggest an association between the cerebellar ataxia and poliomyelitis virus Type-I infection.

E. H. Johnson

1204. Histological Studies of Coxsackie A7 Poliomyelitis in Man and Monkeys

N. R. GRIST and G. B. S. ROBERTS. *Journal of Pathology and Bacteriology* [J. Path. Bact.] **84**, 39-44, 1962. 6 figs., 12 refs.

In 1959, a year in which infection due to poliomyelitis viruses was virtually absent from Scotland, an outbreak of Coxsackie A7 virus infection occurred. In most of the confirmed cases, 37 in all, there were signs of meningitis without disturbance of motor function, but in 7 children paralysis of a poliomyelitis-like character developed, affecting one or more limbs in 6 and the face in one. Of these 7 children, one, a boy of 10 months, died. He became ill with vomiting and inflammation of the throat 2 weeks after receiving a first dose of inactivated poliomyelitis vaccine into the right deltoid region. Encephalitis and weakness of the right arm developed, followed by circulatory collapse and death within 3 days of the onset of the illness. Histological examination of the brain showed lesions in the pons and medulla indistinguishable from those seen in poliomyelitis virus infection, but only Coxsackie A7 virus (strain 1431) could be isolated from the faeces.

This strain and another (1034) isolated from an infant in whom facial paralysis developed were inoculated intracerebrally into rhesus monkeys, an extract of the human faeces being used. Both animals became excitable and developed tremors about the 9th or 10th day; weakness of the limbs followed with, in one of the animals, a left facial paresis. Both were then killed and histological examination of the brains revealed lesions in the cord and brain-stem similar to those found in the child who died. The medulla of one monkey was shown to contain Coxsackie A7 virus by inoculation of an extract into suckling mice, but no poliomyelitis virus could be detected on inoculation of the extract into cultures of monkey kidney and human thyroid tissue. Sera collected before inoculation and at the time of death showed the development of antibodies at low titre to Coxsackie A7 but not to poliomyelitis virus.

The authors suggest that the term "acute anterior poliomyelitis" describes a clinical and pathological condition which can no longer be considered specific for infection with the classic three types of poliomyelitis virus.

A. Ackroyd

1205. Mass Immunization with Sabin and Cox Oral Poliomyelitis Vaccines: Experience in Monroe and Tompkins Counties, New York, 1960

M. L. RATHBUN, R. H. BROAD, W. FONT, S. MILHAM, and W. R. AMES. *New York State Journal of Medicine* [N.Y. St. J. Med.] **62**, 1767-1775, June 1, 1962. 6 refs.

Mass oral immunization against poliomyelitis was carried out in 1960 in two counties in New York State. Three doses of monovalent Sabin oral vaccine were administered to about 100,000 residents of Monroe County, mostly those of pre-school or school age. In Tompkins County a single dose of Cox trivalent oral vaccine was given to nearly 30,000 indi-

viduals, including adults and children. Both vaccines were tasteless and easily administered. There was some evidence of reaction following administration: a few cases of urticaria after the Sabin vaccine, possibly associated with the penicillin content, and during the campaign a short gastro-intestinal upset was prevalent in Tompkins County, a number of subjects complaining of this after vaccination.

During the "season" following the campaign a few cases of paralytic poliomyelitis occurred in Monroe County, but there were no cases among those who had received the oral vaccine. An attempt to find the effect on antibody titre was difficult. Generally it seemed that Type-I Sabin and Type-III Cox were excellent both as original vaccines and as boosters after a previous Salk injection. Type-III Sabin and Type-II Cox were much less effective!

The authors question whether, in the event of an epidemic, the determination of virus type and the mass feeding of the type-specific vaccine could be carried out in time to affect the course of the epidemic:

E. H. Johnson

1206. Antibody Response to Two Different Live Poliomyelitis Virus Vaccines

J. HOTCHIN, H. PLAGER, W. DECHER, and J. JACOBS. *New York State Journal of Medicine* [N.Y. St. J. Med.] **62**, 1776-1783, June 1, 1962. 2 figs., 7 refs.

In the mass poliomyelitis vaccination campaigns in Monroe and Tompkins Counties of New York State, a monovalent Sabin vaccine being used in the former and a trivalent Cox vaccine in the latter, a systematic double-blind controlled titration of pre- and post-vaccination blood specimens from volunteers in the cities of Rochester and Ithaca allowed the two vaccines to be compared. The results are based on 601 serum pairs, 285 after administration of Sabin vaccine and 316 after administration of the Cox vaccine. Notice had to be taken of the age differences and of the difference in time since vaccination in that there were 3 doses of Sabin to only one of Cox.

Types I and II Sabin were good at all ages, giving a four-fold increase in titre in 71% and 72% of cases respectively. Results were not so good for Type III—only 56.9%. This result was the same for all ages. Cox vaccine Type III was particularly good in children under 10 years, giving a four-fold increase in 90% of cases, but the effect of Types I and II was much less satisfactory. Both vaccines were particularly effective after a previous Salk injection or injections which had not resulted in a raised titre. Thus they satisfactorily eliminated antibody gaps following previous Salk inoculation.

E. H. Johnson

1207. Recent Results of Mass Immunization against Poliomyelitis with Koprowski Strains of Attenuated Live Poliovirus
S. A. PLOTKIN. *American Journal of Public Health and the Nation's Health* [Amer. J. publ. Hlth] **52**, 946-960, June, 1962. 1 fig., 10 refs.

In the period 1959-61 vaccination with Koprowski Type-I and Type-III live attenuated poliomyelitis viruses was administered to 8½ million Polish and Croatia children aged 6 months to 14 years. In Poland in 1958 there had been a major epidemic of poliomyelitis of over 6,000 cases. In the post-epidemic year, 1959, and again in the spring of 1960 two inoculations of killed virus vaccine had been given to a majority of the children. In order to estimate the effect of the live attenuated vaccine elaborate calculations were,

therefore necessary, based on the titres in random samples of serum from children of various ages in the different provinces. Both in Poland and Croatia the number of cases of paralytic poliomyelitis fell markedly in 1961. Particularly striking was the absence of the expected peak of cases in the summer, this being "unparalleled in the epidemiological records of Poland". It was calculated that the conversion rates for sera which were negative to Type I and Type III before oral vaccination were better than 90%, and that the epidemiological efficacy, or degree of prevention of paralytic poliomyelitis, was in the region of 90%.

H. Stanley Banks

1208. Serologic Response of Nonimmune Subjects to Commercial Salk Vaccine: Response and Antibody Persistence with Four Doses

M. L. LEPOW, D. H. CARVER, and F. C. ROBBINS. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 103, 803-811, June, 1962. 5 figs., 24 refs.

Paralytic poliomyelitis continues to occur in apparently well-immunized subjects. The present authors suggest a probable explanation based on the results of a serological study of the responses of 57 completely non-immune children who were aged 6 to 24 months when given the first of 4 doses, over a 26-month period, of a representative commercial Salk vaccine available in America between 1957 and 1959. The children received two doses of vaccine with an interval of one month between each, a third dose 7 months later, and a fourth 18 months after the third. They were followed up for a further 26 months.

There was considerable variation in the primary responses and persistence of antibody to the three components of the vaccines. Type II was the most effective and all the children were serologically immune to this type after the third dose. After 4 doses, the Type-I antibody titre stabilized at a level high enough to indicate that protection would last for a considerable time. Only 2 children had no detectable antibody to this type 26 months after the fourth dose. The antigenic potency of the Type-III component was low and within a year of the fourth dose at least one-fifth of the children lacked protection to this type. Even immediately after the fourth dose the mean titre of the group for Type III was only 192 compared with a mean titre for Type II of 900.

It would thus appear that inadequate antigenic potency, especially of the Type-III component, of vaccines used up to 1959 for primary vaccination was responsible for the lack of protection. This, it is hoped, has now been remedied, so that "with vaccines of proper potency long-lasting immunity to poliomyelitis can be achieved without the need for more than an infrequent booster injection".

A. Ackroyd

1209. A Clinical, Epidemiologic and Laboratory Investigation of Aseptic Meningitis during the Four-year Period, 1955-1958. I. Observations Concerning Etiology and Epidemiology

M. L. LEPOW, D. H. CARVER, H. T. WRIGHT JR., W. A. WOODS, and F. C. ROBBINS. *New England Journal of Medicine* [New Engl. J. Med.] 266, 1181-1187, June 7, 1962. 26 refs.

The authors analyse the results of virological and epidemiological studies in a series of 407 patients admitted to the Metropolitan General Hospital, Cleveland, Ohio, between 1955 and 1958 inclusive with a diagnosis of aseptic

meningitis. Cases of paralytic poliomyelitis, acute demyelinating encephalomyelitis, and post-infection encephalitis were excluded, as were cases in which parotitis was present on admission. Specimens of faeces from all the patients were examined by inoculation of cultures of monkey kidney tissue, and in many cases the cerebrospinal fluid and throat swabs were also examined. Serological examination was restricted to neutralization tests against poliomyelitis virus and complement-fixation tests with mumps antigens. A specific viral cause was established in 54% of the cases. The percentage due to poliomyelitis virus infections declined from 12 to 4 during the period, while the percentage due to other enteroviruses remained unaltered at about 40 each year. Mumps-virus infections accounted for the remainder, although there were 14 instances of dual infections.

The significance of enterovirus isolation from the faeces was gauged during 1957 when 408 healthy subjects were examined, 87 of whom were matched with patients from the total of 98 admitted to hospital that year with aseptic meningitis. Virus was isolated from 7.5% of the healthy subjects compared with 44% of the patients with meningitis. In only one patient among 72 with various other diseases in hospital at the same time was an enterovirus isolated from the faeces. An enterovirus was isolated from 41 out of 286 specimens of cerebrospinal fluid. Whereas most patients with Coxsackie-B virus in the cerebrospinal fluid also harboured the virus in the pharynx or intestinal tract, less than half of those whose fluid yielded an E.C.H.O. virus were found to harbour the virus in the throat or faeces. No virus was isolated from 150 specimens of normal cerebrospinal fluid.

There were 11 families in which 2 or more members had aseptic meningitis. Subclinical infection in household contacts was demonstrated by detecting the same type of enterovirus in the contacts of 18 out of 21 patients from whom virus was isolated. Of 27 patients from whom no virus was isolated, virus was demonstrated in the home contacts of 4 of them.

The authors recognize that the laboratory procedures used in this study were limited and did not provide information concerning the possible role of the Coxsackie-A viruses, lymphocytic choriomeningitis virus, the arbor viruses, or the leptospira as causative agents of the aseptic meningitis syndrome.

[No account seems to have been taken of the possibility that herpes simplex virus may have been the cause of a proportion of the cases.]

J. E. M. Whitehead

1210. A Clinical, Epidemiologic and Laboratory Investigation of Aseptic Meningitis during the Four-year Period, 1955-1958. II. The Clinical Disease and Its Sequelae

M. L. LEPOW, N. COYNE, L. B. THOMPSON, D. H. CARVER, and F. C. ROBBINS. *New England Journal of Medicine* [New Engl. J. Med.] 266, 1188-1193, June 7, 1962. 16 refs.

The clinical features of the syndrome of aseptic meningitis as manifested in 407 patients admitted to the Metropolitan General Hospital, Cleveland, Ohio, are described. [For the epidemiological and virological aspects of this series of cases see Abstract 1209.] The onset of the disease was accompanied by headache, vomiting, fever, and stiffness of the neck. From 15 out of 48 patients who complained of chest or abdominal pain, a virus of Coxsackie Group B was isolated. In 5 cases there was a complaint of sore

throat or rhinitis. Of 7 patients with a rash, E.C.H.O. virus Type 9 was isolated from 2. The illness lasted less than 2 weeks in most cases. More severe illness was seen in 45 patients, 12 of whom had general and 2 had focal convulsions. Coma or severe lethargy was observed in 15 other patients. Blurring of the optic disk was seen in 4 patients and transient sensory changes were detected in 3 others. Motor weakness sufficient to call for long-term care and rehabilitation occurred in 4 patients, 3 of whom yielded a virus of the Coxsackie Group B. The cell count in the cerebrospinal fluid (C.S.F.) exceeded 300 per c.mm. in one-third of the cases and in half of these it exceeded 1,000 per c.mm. In two-thirds of the patients there was a predominance of polymorphonuclear leucocytes in the C.S.F. Mumps virus infections, however, were associated with high counts and the cells were predominantly mononuclear.

A total of 301 patients were followed up, those with more severe illness and those with a history of previous disease of the central nervous system being excluded. On discharge from hospital 30% were completely well and remained so. Among the 179 who returned for examination in 3 months about 50% manifested subjective or objective symptoms. Fatigue, irritability, and lack of concentration were common complaints. Objective signs of limitation of passive movements by muscular stiffness or of definite muscular weakness were observed in about three-quarters of the group. However, over 95% had recovered within a year.

J. E. M. Whitehead

1211. Virologic and Clinical Observations on Cytomegalic Inclusion Disease

T. H. WELLER and J. B. HANSHAW. *New England Journal of Medicine* [New Engl. J. Med.] 266, 1233-1244, June 14, 1962. 5 figs., 34 refs.

Understanding of the pathological significance of the cytomegaloviruses (salivary-gland viruses) in human disease has been hindered by the technical difficulties of cultivating the viruses, their antigenic variety, and their apparent ubiquity in certain population groups. In this paper from Harvard School of Public Health and the Children's Hospital, Boston, the clinical and virological findings in 17 infants suffering from cytomegalic inclusion disease are reviewed. Isolation of the virus from the urine by inoculation of cultures of rolled primary human embryonic skin-muscle tissue was successful in 16 cases; in one case virus was isolated from a liver biopsy specimen, the only source of virus available. In some cases the cytopathic effect did not develop until 28 days after inoculation of the tissue cultures. Repeated positive cultures from the urine were obtained in 13 cases, often for periods of many months, and in one instance for 52 months. No virus was recovered from single or multiple specimens of urine from 136 patients in hospital suffering from illnesses sharing a common sign or symptom with cytomegalic inclusion disease, except in one patient with chronic candidiasis whose urine yielded virus and in whom there was minimal enlargement of the liver and spleen. Persistent hepatosplenomegaly was observed in all 17 infants, 11 of whom were also jaundiced and 9 of whom exhibited haemorrhagic manifestations. Chorioretinitis was present in 5 infants and there was evidence of cerebral calcification in 4. Microcephaly occurred in 14 infants; in 5 it was present at birth and in 2 it developed during the second year of life. One of the 17 infants died in the third year of life and 14 of the survivors showed

sequelae, 13 being mentally retarded, 6 severely so. Varying degrees of motor disability were observed in 12. The authors also studied 10 infants in whom liver biopsy examination revealed histological changes suggestive of "neonatal hepatitis"; a cytomegalovirus was isolated from the urine or biopsy specimen in 5 of these patients.

[It is impossible in an abstract to do justice to this excellent review of the clinical and virological problems of this disease.]
J. E. M. Whitehead

1212. An Epidemiologic Study of Mumps; Its Spread in Schools and Families

M. B. MEYER. *American Journal of Hygiene* [Amer. J. Hyg.] 75, 259-281, March, 1962. 10 figs., 35 refs.

This valuable study from the Johns Hopkins University School of Hygiene and Public Health, Baltimore, provides new information on the epidemiology of mumps. It is based on epidemics of mumps in 5 private schools in Baltimore and in the families of children attending these schools; careful attention was paid to dates of contact and of onset and to the modes of contact between individuals. A total of 371 cases, observed over periods up to 2 years, were studied and the data were thoroughly analysed.

The findings indicate that mumps is spread through the community by way of school-children; with secondary spread to other members of the families concerned; thence siblings of school age continue the spread via their own schools and classes. The pattern of spread of mumps is essentially similar to that of measles when account is taken of certain differences between the two diseases, especially the high incidence of inapparent infection in mumps (up to 40%), while in measles almost all the infections are clinically apparent. Other important differences which tend to mask the high infectivity of mumps include: (1) the longer incubation period of mumps, the median interval between cases being 18 days, compared with 12 days in measles; (2) the rarity of clinically apparent mumps in children under 3 years of age, with corresponding frequency of inapparent attacks at this age resulting in complete immunity or partial immunity which may be short-lived; and (3) the probability of a short period of high infectivity in mumps for a few days before the onset of symptoms, in contrast with the infective period of measles, which begins with the onset of symptoms.

H. Stanley Banks

1213. The Pathogenesis of Psittacosis. Serial Studies on Rhesus Monkeys Exposed to a Small-particle Aerosol of the Borg Strain

M. H. MCGAVRAN, C. W. BEARD, R. F. BERENDT, and R. M. NAKAMURA. *American Journal of Pathology* [Amer. J. Path.] 40, 653-670, June, 1962. 22 figs., 16 refs.

The pathogenesis of psittacosis was studied in 24 anaesthetized rhesus monkeys exposed to a small-particle aerosol of the Borg strain of psittacosis virus in a laboratory of the U.S. Army, Fort Detrick, Frederick, Maryland. Evidence of infection was sought in the rectal temperature (taken daily), chest radiographs, the results of serum complement-fixation tests, and the findings at serial necropsies on animals killed at intervals up to 37 days. None of the monkeys died from psittacosis. The initial site of infection was in the respiratory bronchiole with subsequent contiguous centrifugal spread resulting in lobular pneumonia by the 14th to 16th days. The inflammatory reaction comprised

a mononuclear-cell exudate rich in fibrin with epithelial hyperplasia at the advancing edge of infection; it was intraluminal rather than interstitial. Resolution, which began after 16 days and was complete by the fifth week, was characterized by disappearance of neutrophil granulocytes, replacement of mononuclear leucocytes by macrophages, and a nonspecific peribronchial and perivascular interstitial reaction. During the infection the monkeys remained well, but were febrile between the tenth and fifteenth days; complement-fixing antibodies developed in the serum in the second and third weeks.

Psittacosis virus was found in the lung for 3 weeks, even after maximum levels of serum antibodies had been attained; it was isolated for shorter periods from tracheobronchial lymph nodes, blood, liver, and spleen.

D. Geraint James

1214. Serum Hepatitis from Transfusions of Blood

J. G. ALLEN and W. A. SAYMAN. *Journal of the American Medical Association [J. Amer. med. Ass.]* 180, 1079-1085, June 30, 1962. 3 refs.

Certain factors influencing the occurrence of hepatitis following blood transfusion were studied in a random sample of 21.4% of 11,627 patients given transfusions during the decade 1946-56 at the University of Chicago Clinics. In just over one-half of the patients in whom serum hepatitis developed the incubation period ranged from the 30th to the 60th day after transfusion. The over-all attack rate for all patients receiving blood was 3%. The number of transfusions received by a patient was a more important factor than age, blood group, race, or sex. Women received more transfusions than men, this being explained by the frequency with which they were given during gynaecological operations, for puerperal haemorrhage, and in women subjected to mastectomy. No deaths attributable to serum hepatitis occurred in patients under the age of 36 years, but the mortality among those in whom hepatitis developed after the age of 40 years was 23%. The over-all mortality for all patients receiving blood was 0.9%.

The authors conclude that there is a great need for a simple test to detect the blood donor who is a carrier of the hepatitis virus.

D. Geraint James

BACTERIAL DISEASES

1215. Cross-infection: Its Control in an Orthopaedic Hospital by Means of a Cubicled Isolation Ward

C. H. LACK, A. G. TOWERS, and F. H. STEVENSON. *Lancet [Lancet]* 1, 1228-1231, June 9, 1962. 4 figs., 3 refs.

This is an important contribution to the very large problem of the control of staphylococcal and other cross-infection in hospitals. The staff of the Royal National Orthopaedic Hospital, Stanmore, Middlesex, plagued by many post-operative infections due to hospital staphylococci, revised their dressing techniques, abolished dry sweeping, and introduced other theoretical measures for the reduction of cross-infection. The very limited results obtained with such measures convinced them that isolation of infection was necessary, and some 2 years ago an isolation ward of 17 rooms, with a control 6-foot corridor, was constructed from an existing open ward. [This is probably the cheapest form of isolation ward that can be made available rapidly and on a

wide scale in existing hospitals, and it is open to weighty theoretical criticism. For example, it must be admitted that air currents from the corridor may convey staphylococci into the cubicles. In Sweden great expense has been incurred, as well as maintenance difficulties, by the construction of isolation blocks with air locks between corridor and rooms, and the practical question arises whether or to what extent such expensive provision is necessary.]

The success now reported from Stanmore—an abrupt reduction in the percentage of postoperative septic (staphylococcal) cases from a more or less steady 5% before 1959 to 1.02% in 1961, and a similar reduction in the proportion of penicillin-resistant staphylococci isolated—serves to indicate the sort of improvement that can be achieved by the skilled and intelligent use of the degree of isolation possible in such a reconstructed ward. The nursing and other details of technique applied to the daily running of this isolation ward are briefly but adequately set out, and nothing could more clearly show the need in this type of work for skilled direction based on laboratory findings and for a trained staff to carry out the rules.

Some valuable bacteriological investigations on the patients, the staff and their clothes, and the rooms and their contents were made. As a result of the knowledge so acquired certain techniques were omitted and others tightened up. For example, under the conditions present, nasal carriage by the staff was not found to be a problem; the use of plastic aprons soaked in 0.1% chlorhexidine and hung to dry under a hot-air fan was upheld; and the role of nurses' uniforms, books, vacuum-cleaner, and blankets in the conveyance or non-conveyance of infection was defined. A finding that must be emphasized is that no spread of any one staphylococcus occurred from room to room. This is a remarkable tribute to the efficiency with which this particular unit was run during the trial period of 2 years.

H. Stanley Banks

1216. Repair after Gangrene Due to Waterhouse-Friderichsen Syndrome

Z. NEUMAN, J. SHULMAN, and S. KEDAR. *American Journal of Diseases of Children [Amer. J. Dis. Child.]* 103, 822-826, June, 1962. 9 figs., 15 refs.

This paper from Rothschild-Hadassah University Hospital, Jerusalem, describes the surgical repair of post-gangrenous lesions "due to Waterhouse-Friderichsen (W.F.) syndrome". [However, in the abstracter's opinion, the 3 cases mentioned have not been clearly shown to be examples of this syndrome.] In the first case a girl aged 5 years had meningococcal septicaemia with a profuse petechial rash and many ecchymoses 2 to 4 mm. in diameter scattered over the face and body. [Whether the blood pressure (60/40 mm. Hg) and the pulse rate (140 to 160 per minute) were sufficient evidence of the extreme shock that would permit classification as W.F. syndrome is impossible to determine from the data supplied.] The skin lesions illustrated in this case (petechiae, purpuric areas, and button-like indurations and necroses) are quite characteristic of the severe ordinary form of meningococcal septicaemia, although they may also occur in the W.F. syndrome. In Case 2, that of a boy of 8, there was a history of meningococcal septicaemia 5 years previously [no mention of W.F. syndrome]; and Case 3 seems to have been one of varicella gangrenosa 11 years earlier with subsequent gangrene of the extremities and extensive amputations.

The surgical treatment described seems to have effected considerable improvement in these cases. The skin sloughs that may be associated with a profuse meningococcal rash usually heal well with conservative treatment, but in Case 1 the size of the ulcers left after separation of the sloughs seems to have justified skin-grafting, while the smaller lesions were excised and sutured. In Case 2, where flexion contractures of the fingers had ensued, the scar tissue was excised, a Z plasty performed, and the bare area skin-grafted. In Case 3 deformed united fingers were separated from one another and skin-grafted.

H. Stanley Banks

1217. Electrolyte Metabolism in Tetanus. (Sul ricambio elettrolitico nella infezione tetanica)

A. COMPARINI and G. RANIERI. *Ospedali d'Italia-Chirurgia [Osped. Ital.-Chir.]* 6, 473-483, April [received July], 1962. 35 refs.

The authors, working at the Santa Maria Nuova Hospital, Florence, investigated the metabolism of the electrolytes (chlorides, sodium, and potassium) in 10 cases of tetanus, and carried out certain biochemical investigations on the blood and urine. During the acute period of the infection they observed retention of the chloride and sodium electrolytes. The potassium level in the blood and in the urine was normal. A slight increase in the plasma proteins, especially the γ -globulins, was noted between the 4th and the 12th days. The authors recommend thorough biochemical investigation of each case before treatment is begun.

Franz Heimann

1218. Inefficiency of Purified Diphtheria Formol Toxoid in Primary Immunization against Diphtheria

MEDICAL RESEARCH COUNCIL COMMITTEE ON DIPHTHERIA TOXOID. *British Medical Journal [Brit. med. J.]* 2, 149-151, July 21, 1962. 9 refs.

In order to assess the immunizing efficacy of the diphtheria plain formol toxoid, 5 separate trials were carried out in children, 6 to 12 months old, who were brought to clinics for routine immunization against diphtheria. In each trial formol toxoid was given, but the doses and the intervals between doses differed with each trial. Formol toxoid was administered subcutaneously and the immunizing response was assessed by antitoxin titration of samples of serum.

In all the trials there was a very poor and inadequate immunizing response, and it is concluded that diphtheria plain formol toxoid in its highly purified form is not suitable for primary immunization against diphtheria. To obtain adequate primary immunization this purified antigen must be combined with an adjuvant such as pertussis vaccine or a mineral carrier such as aluminium hydroxide or phosphate.

John Fry

1219. Typhoid Carriers, with Special Reference to Patients Treated with Chloramphenicol. (Beiträge zur Frage der Typhusbazillendauerausscheider mit besonderer Hinsicht auf die mit Chloramphenicol behandelten Typhuskranken)

D. MÜNNICH. *Zeitschrift für die gesamte innere Medizin und ihre Grenzgebiete [Z. ges. inn. Med.]* 17, 424-431, May 15 [received July], 1962. 4 figs., 15 refs.

Among 466 patients who had been treated for typhoid fever at the Hajdu-Bihar District Hospital, Debrecen, Hungary, between 1949 and 1960, the author found 19 carriers (4%). Of the 310 who had been treated with chlorampheni-

col, 2 (0.7%) had died and 18 (5.8%) had become carriers, while of the 156 who had not been so treated, 24 (15.4%) had died and only one had become a carrier. Factors favouring the development of the carrier state are, in the author's view, too low dosage of chloramphenicol, administration of the drug over too short a period, and the presence of disease of the gall-bladder and biliary passages. Typhoid bacilli tend to persist in the body and relapses to occur in such cases. The most suitable time for beginning treatment with chloramphenicol is during the second week of the disease. Prophylactic inoculation, passive immunization with γ -globulins, and adequate treatment with chloramphenicol help to reduce the number of carriers. Franz Heimann

1220. Food Hygiene on Board Ship

B. C. HOBBS, J. M. RITCHIE, and E. D. RITCHIE. *Journal of Hygiene [J. Hyg. (Lond.)]* 60, 259-278, June, 1962. 12 refs.

An investigation into food hygiene on a luxury liner during a Mediterranean cruise and on a smaller ship making a 3-month voyage round the tropics is described in this paper from the Central Public Health Laboratory, London. A bacteriological laboratory was installed in each ship for the purpose of the investigation. The principal findings and recommendations made to the shipping company are summarized as follows. Drinking-water shipped at all ports, including those in Britain, should be chlorinated immediately after the water is taken aboard, since the hoses making connexion with the mains are liable to be contaminated. Faults in ice-making machines may be responsible for grossly contaminated ice and iced water; these machines should be frequently examined. Liquid milk should be shipped in 5-gallon (22.7-litre) churns; these are convenient for handling on board and should not be used again during the voyage. Swimming-bath water should be chlorinated in the tropics, even when changed twice daily. Dried products such as ice-cream powder, coconut, and dried or frozen eggs should be of good bacteriological quality and free from *Salmonellae*. Cooked crayfish should not be split in the raw-fish department, but on a clean, impermeable surface elsewhere. [Crayfish salad can be a frequent source of food poisoning.] During the preparation of imitation cream special attention should be paid to the hygiene of the hands. Savoy bags for storing and for piping cream should be of plastic or nylon and should be boiled thoroughly after being cleaned. Salads and dessert fruit should be washed in water containing 80 p.p.m. of sodium hypochlorite. Dish covers, which are apt to harbour small quantities of contaminated food, should be washed and sterilized regularly. Washing-up water in machines should be maintained at a temperature of 70° to 80° C.; otherwise, a strong bactericidal detergent is required. Cloths and cutting boards used in the galley should be soaked overnight in a solution of sodium hypochlorite.

On the Mediterranean cruise 54 cases of gastroenteritis were reported. Neither *Salmonellae* nor *Shigellae* were found, but heat-resistant *Clostridium welchii* was isolated from 6 of the 28 faecal specimens examined, and the clinical picture was that of *Cl. welchii* poisoning—namely, diarrhoea and abdominal pain, in most cases without vomiting and pyrexia.

[This is a much-needed investigation.]

H. Stanley Banks

Tuberculosis

1221. **Critical Study on 40 Children Previously Vaccinated with B.C.G., Admitted with a Diagnosis of Tuberculosis.** (Étude critique de 40 observations d'enfants admis avec le diagnostic de tuberculose initiale, antérieurement vaccinés par le B.C.G.)

J. GERBEAUX and J. HEBERT-JOUAS. *Archives françaises de pédiatrie* [Arch. franç. Pédiat.] 19, 219-230, Feb. [received May], 1962. 2 refs.

The authors describe a study of 40 infants with a history of B.C.G. vaccination who later developed tuberculosis on exposure to natural infection, special attention being paid to the adequacy of the technique of vaccination and the subsequent post-vaccination tuberculin sensitivity.

In one group of 17 infants the initial diagnosis of tuberculosis was probably incorrect. In 6 others the technique used had been inadequate. In a further 12 infants the tuberculin sensitivity had disappeared before exposure to the natural infection, and in 3 the sensitivity had been very weak when exposure occurred. In only 2 cases did adequate sensitivity after vaccination persist at the time of the natural infection.

In the authors' experience most of the cases of tuberculosis in B.C.G.-vaccinated children occur either in those who have not been rendered tuberculin-sensitive by the vaccine or in those in whom the sensitivity has disappeared at the time of contact with the natural infection responsible for the disease.

T. M. Pollock

1222. **The Effect of Isoniazid Prophylaxis on Tuberculosis Morbidity Among Household Contacts of Previously Known Cases of Tuberculosis**

F. W. MOUNT and S. H. FEREBEE. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 821-827, June, 1962. 1 ref.

A study of the prophylactic value of isoniazid in household contacts of 802 previously known cases of tuberculosis is reported from the United States Department of Health, Education, and Welfare, Washington. Of 2,814 contacts 1,351 were given a placebo and 1,463 received isoniazid. The dosage depended on age, adults being given 300 mg. daily (approximately 5 mg. per kg. body weight) for a year. Approximately 48% of the contacts given a placebo and 46% of those given isoniazid took the drugs faithfully for the entire year. During the year 3 taking isoniazid developed active tuberculosis (primary in one, pleural effusion in one, and pulmonary in one) compared with 9 (primary in 2 and pulmonary in 7) taking the placebo. In the 3 years since the year of the trial 3 further cases of tuberculosis have become known in each group.

G. M. Little

1223. **Tuberculosis in Man, Dog, and Cat**

V. M. HAWTHORNE and I. M. LAUDER. *American Review of Respiratory Diseases* [Amer. Rev. resp. Dis.] 85, 858-869, June, 1962. 7 figs., 24 refs.

The authors of this paper from the Western Regional Hospital Board, Glasgow, examined 48 dogs and cats which were contacts of subjects suffering from active tuberculosis.

Mycobacterium tuberculosis was recovered from 4 dogs and 3 cats, the strains isolated being human. At necropsy on 3 of the dogs and on the 3 cats *Myco. tuberculosis* was not recovered. Of 354 contacts of 31 dogs dying from tuberculosis, 41 were found to have evidence of active tuberculosis. In 16 instances the owner or a member of the family showed evidence of tuberculosis and in 7 the probable contact was traced to a neighbour or to a previous owner. The authors emphasize that tuberculous animals should be reported to the public health authorities and that strict hygienic precautions should be taken in tuberculous households where pets have not been prohibited.

The technique of using B.C.G. vaccination as a diagnostic test for detection of tuberculosis in dogs and cats is described. From a comparison of the results with this test with those of the tuberculin test with purified protein derivative, the authors conclude that in this series the former had marked advantages over the latter.

G. M. Little

RESPIRATORY TUBERCULOSIS

1224. **Tuberculosis in Pakistanis in Bradford**

D. K. STEVENSON. *British Medical Journal* [Brit. med. J.] 1, 1382-1386, May 19, 1962. 5 refs.

Since 1954 there has been a considerable increase in the number of Pakistanis living in Bradford. Most of these are males, aged 20 to 40, who work in the combing industry of the wool textile trade. By 1961 the number of cases of tuberculosis in male Asians in the city (about 85% of whom are Pakistanis) was higher than that in all adult males resident in Bradford. The number of cases of tuberculosis in the British population in Bradford in 1961 was 186, giving an incidence, accepting the population as 290,000, of 0.06% per annum; the incidence among the Pakistani population was approximately 1.8% or 30 times higher.

Between 1955 and 1959 an investigation was carried out in Pakistanis admitted to hospital with tuberculosis to determine whether they had active tuberculosis at the time of immigration or whether they developed the disease after entry into Britain. In 33% tuberculosis was diagnosed within 12 months of entry, and in 40% to 50% the chest radiograph was abnormal at the time of immigration.

It is strongly recommended that all immigrants should be subjected to x-ray examination of the chest at the time of entry into the United Kingdom.

T. M. Pollock

1225. **Tuberculosis among Indian Immigrants to a Midland Industrial Area**

J. ASPIN. *British Medical Journal* [Brit. med. J.] 1, 1386-1388, May 19, 1962. 5 refs.

By the end of 1960 there were an estimated 3,000 adult Indian immigrants living in Wolverhampton, equivalent to 2% of the local population. Since January, 1954, tuberculosis has been diagnosed in 62 adult Indians and 5 Pakistanis. The number of new cases of tuberculosis among Indians is increasing each year.

A study of the radiological appearances of the chest and the clinical type of tuberculosis suggested that only about 13 (49%) of the 67 cases would have been revealed by a chest radiograph obtained on entry into Britain. In about 9% of the Indians there was resistance to streptomycin, PAS, or isoniazid, a higher percentage than would be expected in the British population.

It is recommended that all Indians should be subjected to x-ray examination of the chest before they are accepted on the list of a general practitioner and thereafter once a year.

T. M. Pollock

1226. Ethionamide in Association with Isoniazid Infusion in the Treatment of Chronic Pulmonary Tuberculosis. (L'associazione etilisotiamide-isoniazide perfusione nella terapia della tubercolosi polmonare cronica)

T. TODOROFF, A. VIGONI, and F. GIACOMUZZI. *Minerva medica* [Minerva med.] 53, 1523-1526, May 16, 1962. 24 refs.

This is a report of 15 cases of long-standing pulmonary tuberculosis treated at the Cuasso al Monte Sanatorium, Varese, Italy, with ethionamide and isoniazid. All the patients were males and their ages ranged from 35 to 60 years. All had received various forms of antituberculous treatment, to which the organisms responsible for their disease had become resistant. [The drugs previously used are not specified.] *Mycobacterium tuberculosis* was present in the sputum of all the patients. The authors treated them for 60 days with ethionamide 1 g. daily orally for 2 successive days alternating with isoniazid 500 mg. daily by intravenous infusion for 2 successive days. To avoid initial intolerance the dose of ethionamide was only 0.5 g. on the first 2 days of that drug and 0.75 g. on the second 2 days; thereafter 1 g. was given. In nearly all the cases there were signs of gastro-intestinal intolerance, which disappeared if ethionamide was withdrawn for a few days, and were less severe when it was resumed. In one case only was it necessary to stop the ethionamide altogether, because of persistent diarrhoea. At the end of the course *Myco. tuberculosis* could no longer be detected in the sputum of 9 of the cases and the erythrocyte sedimentation rate had become normal in 12. Subjective symptoms, such as cough, were relieved and in some cases improvement in the x-ray appearances was noted. In the authors' view, ethionamide should always be given in association with isoniazid, because crossed resistance between the two drugs does not occur.

J. A. Farfor

1227. Treatment of Tuberculous Primary Infection with Isoniazid and Ethionamide in High Dosage. (Le traitement de la primo-infection par l'association I.N.H.-éthionamide à doses élevées)

A. DE VOOGD and H. FINIELZ. *Revue de tuberculose et de pneumologie* [Rev. Tuberc. (Paris)] 26, 340-352, Feb.-March [received June], 1962. 8 figs.

This paper describes the treatment of 161 children at the Lafayette Preventorium, Haute-Loire, France, over a period of 2 years, with isoniazid and ethionamide in association and in high dosage. The younger children received 25 mg. of isoniazid per kg. body weight and 25 mg. of ethionamide per kg., the older children 10 mg. and 15 mg. per kg. respectively. With a view to preventing side-effects, nicotinamide, pyridoxine hydrochloride, and aneurine hydrochloride were also given, on the supposition that the isoniazid-ethionamide

treatment causes a deficiency of the B-complex vitamins. Tolerance tests are described in detail. Assessment of the efficacy of the treatment is, the authors observe, difficult, both because of the variability in the evolution of the affection and because of the many forms which the lesions may take.

For various reasons, 30 patients were excluded from the study. Of the remaining 131 patients, 107 had recent lesions and 24 had lesions of long standing—that is, of more than 4 or 5 months' duration. "Good" or "very good" results were recorded in 85% of the former group and in 58% of the latter group. The results were a little less satisfactory and much slower in appearing when treatment with isoniazid-ethionamide followed that with isoniazid-PAS or isoniazid-streptomycin. It is therefore important to treat severe forms with isoniazid-ethionamide from the beginning. The authors conclude that the combination of isoniazid and ethionamide is the most effective treatment available. The addition of nicotinamide, pyridoxine hydrochloride, and aneurine hydrochloride appears to be useful in preventing side-effects.

Norman F. Smith

1228. Atypical Mycobacteria and Pulmonary Disease

H. B. GREENBERG and M. CAMPAGNA. *Geriatrics* [Geriatrics] 17, 456-463, July, 1962. 6 figs., 15 refs.

Among patients attending the New Orleans Tuberculosis Clinic between 1958 and 1961 because of x-ray evidence of lung disease or a history of tuberculosis, atypical mycobacteria were isolated from sputum cultures of 40. The patients were almost equally divided between Negroes and Caucasians and the majority were men aged from 41 to 78 years. Photochromogens and the Battey strain of mycobacteria (slow-growing and non-pigmented) were found most commonly, the former occurring in 13 patients and the latter in 15. Skotochromogens were recovered from 12 patients and "rapid growers" from 4.

The patients fell into three groups, the first including 18 who had been treated for proven pulmonary tuberculosis. Progressive disease attributed to atypical mycobacteria occurred in only one case. The appearance of atypical mycobacteria did not seem to follow inadequate treatment, as the majority of patients had received "continuous chemotherapy for 12 months or longer". The second group consisted of 13 patients, observed for more than 3 years, whose chest radiographs had been unchanged and sputum cultures negative for tubercle bacilli until atypical mycobacteria were discovered. In 3 of these patients extensive pulmonary disease occurred, but in the rest there was no "discernible change in pulmonary lesions or clinical status". In the third group extensive lung disease resulted from atypical mycobacteria which were early identified in sputum cultures. There was no history of previous lung disease, and response to chemotherapy was similar to that of patients with acute pulmonary tuberculosis. [Unfortunately, the types of organism in each of these groups are not shown or relationships analysed.]

In 4 patients with extensive pulmonary disease different groups of atypical mycobacteria were found, and in 3 others *Mycobacterium tuberculosis* was found in alternation with atypical organisms.

In their discussion the authors suggest that atypical mycobacteria may well be variants of *Myco. tuberculosis*.

W. Raymond Parkes

Venereal Diseases

1229. The Return of the Venereal Diseases

F. J. G. JEFFERISS. *British Medical Journal* [Brit. med. J.] 1, 1751-1753, June 23, 1962. 4 figs., 8 refs.

The recent increase in the prevalence of venereal diseases in Britain is considered in the light of the Ministry of Health's statistics and the studies of the British Cooperative Clinical Group, but particularly from the returns of a London clinic (St. Mary's Hospital) situated in an area in which large numbers of West Indian and other immigrants reside.

"By far the greatest" cause of the increase in venereal diseases since 1955 is considered to be immigration. In 1960 at St. Mary's only 30% of male patients with gonorrhoea were born in the United Kingdom; 40% were West Indians, 10% of other coloured races, and 20% of other groups. The next most important cause of the increase in venereal diseases in London is considered to be the male homosexual, 70% of patients with early syphilis who attended St. Mary's Hospital in 1961 admitting to homosexual contact. [The figures for gonorrhoea are not given.] The third cause is said to be the increase of promiscuity among young persons. At St. Mary's Hospital 37% of cases of gonorrhoea in teenage males affected those born in the United Kingdom (a higher figure than the 30% of the total cases), from which it is concluded that, if the situation in the rest of the country were similar, then much of the increase of gonorrhoea in this group is accounted for by young immigrants. The opinion is expressed, on the reasoning that approximately one male teenager to 2 females was treated for gonorrhoea in the clinic in 1960—a greater proportion of females than the nearly 4 to 1 encountered for all ages in all clinics—"that the greater part of the increase of venereal disease among young people is due to their association with immigrants of all colours, and to the general increase of venereal disease caused by the latter, making promiscuous youth more liable to infection". That drug resistance is a reason for the increase is considered to be a fallacy.

Methods recommended to check the increase include health education, limitation of immigration, proper housing provision for immigrants, and the repatriation of immigrants convicted for sexual crimes.

[The British Cooperative Clinical Group studies referred to have shown, if anything, a lower proportion of teenagers in the clinics, with a majority of West Indian male immigrants, than in the rest of the country.] R. R. Willcox

1230. Treatment of Gonorrhoea with Actinospectacin

S. M. LAIRD and G. TAYLOR. *British Journal of Venereal Diseases* [Brit. J. vener. Dis.] 38, 60-63, June, 1962. 2 refs.

The authors, at the Royal Infirmary, Manchester, used actinospectacin ("trobicin"), an antibiotic produced by *Streptomyces spectabilis* n.s., in the treatment of 67 males suffering from gonococcal urethritis. A single injection of 2 g. of the antibiotic dissolved in 5 ml. of distilled water resulted in cure in 47 of 50 cases. With a single injection of 1 g. in 2.5 ml. of distilled water cure was obtained in only 11 out of 16 cases. These cure rates were calculated on

the assumption that patients who did not return for examination after treatment were cured. There were 10 such patients in the first group and 2 in the second. In one patient given 0.5 g. of actinospectacin no improvement was noted.

The minimum concentration of actinospectacin required to inhibit the growth of the gonococcus was estimated in 37 cases before treatment and in 5 cases after re-isolation of the gonococcus following unsuccessful treatment. In 2 of the 5 cases there was a marked rise in the minimum inhibitory concentration after 1 g. of actinospectacin had failed to cure the disease. There were no untoward general reactions to treatment, but 3 patients complained of local discomfort at the site of injection.

It would appear that actinospectacin is an effective alternative to penicillin in the treatment of gonorrhoea [but its use should be limited to carefully controlled series]. The authors consider that it should be of value in cases due to gonococci with increased resistance to penicillin and streptomycin and in patients hypersensitive to these antibiotics.

Eric Dunlop

SYPHILIS

1231. Seronegativity in Primary Syphilis. (Sulla carenza sierologica nella sifilide primaria attuale)

S. D. RANDAZZO. *Minerva dermatologica* [Minerva dermat.] 37, 139-144, April [received June], 1962. 26 refs.

The author, writing from the University of Catania, Sicily, describes 183 cases of primary syphilis in many of which seropositivity developed later than the 25th day, or not at all. The age, sex, and occupation of the patients and the site of the primary lesions are summarized. Multiple primary lesions were present in 2 women and in 36 men, and in a further 50 cases the primary lesions were otherwise atypical. In all the cases the history, the clinical examination, and the dark-ground examination put the diagnosis of syphilis beyond doubt.

In 67 (36%) of the cases serological tests were negative at the time of the appearance of the primary lesion, although regional lymphadenopathy was present and the dark-ground findings were positive. In 25 of these cases the serological reactions were still negative on the 70th day and did not become positive until the first signs of the secondary stage appeared. Provocative and, later, curative specific treatment produced seropositivity in a further 16 cases within 180 days of the appearance of the chancre. Finally, 9 cases remained seronegative over 180 days, although specific treatment produced a Heixheimer reaction and other effects. In 2 of these 9 cases the treponemal immobilization (T.P.I.) test was positive from the 30th day; in the remaining 7 the T.P.I. test and the classical serological tests remained negative for over 180 days. The citochol reaction was the first to become positive, followed by the Kahn and microgen reactions. The Wassermann reaction became positive, both with cardiolipin and beef heart antigens, 7 to 10 days after the citochol reaction.

In the other 116 cases (64% of the series) the classic serological tests were positive in the primary stage; the T.P.I. test was positive in 8 cases, doubtful in 14, and negative in 94.

The author discusses these findings in relation to published work. Factors which may play a part in persistent seronegativity are the antibody-forming capacity of the patient, the antigenicity of the organisms, and the insensitivity of the available tests. In the 9 cases which remained seronegative for 180 days the serological reactions may have been affected by the treatment, which in their case was started on the 70th day. The frequency of prolonged seronegativity must not be allowed to lead to a false sense of security on the part of the patient or to become a danger to the public health.

F. Hillman

1232. **The Problem and Importance of False Positive Reactions in Serological Tests for Syphilis.** (Die Problematik und die Bedeutung der unspezifisch positiven Reaktionen in der Lues-Serologie)

A. KERN. *Dermatologische Wochenschrift* [Derm. Wschr.] 145, 633-655, June 23, 1962. 8 figs., bibliography.

In recent years there has been increasing interest in the specificity of serological tests for syphilis, and since the discovery of the treponemal immobilization test by Nelson and Mayer in 1949 it has become possible to distinguish with considerable accuracy between specific and non-specific reactions. The diminishing incidence of syphilis in many countries has produced a relative increase in the number of cases with non-specific reactions and heightened the importance of accurate diagnosis in patients in whom serological tests give positive results. The fact that some of the subjects who have non-specific reactions eventually develop serious disease, usually in the form of systemic lupus erythematosus or other collagen disease, lays a new responsibility on the venereologist investigating patients with positive serological reactions. Knowledge in this field of medicine has advanced slowly but steadily and the literature is voluminous. A thorough review of the relevant literature of the last 50 years is therefore welcome. This paper from the Karl Marx University, Leipzig, covers the subject in great detail and gives a clear and accurate account of the work on which the present concept of the biological false positive reaction is based. There is an interesting discussion on the possible mechanism of the anomaly and on its causes. [The bibliography of 168 items is exhaustive and the paper is most useful for purposes of reference.]

R. D. Catterall

1233. **The Action of Penicillin in Late Syphilis: Persistence of *Treponema pallidum* after Treatment. Part I. Experimental Syphilis.** (Étude de l'action de la pénicilline dans la syphilis tardive: persistance du tréponème pâle après traitement. Première partie. La syphilis tardive expérimentale) P. COLLART, L. J. BOREL, and P. DUREL. *Annales de l'Institut Pasteur* [Ann. Inst. Pasteur] 102, 596-615, May, 1962. 8 figs., 13 refs.

This is a study, from the Alfred Fournier Institute, Paris, of the persistence of *Treponema pallidum* in 50 rabbits infected with the Nichols strain of that organism and treated with benzathine penicillin.

The treponemal immobilization (T.P.I.) test was negative in all the animals before inoculation. The progress of the

disease was observed by repetition of this test and by examination of the lesions and lymph nodes by a special silver-staining technique (which is described). The rabbits were treated, 2 years after inoculation, with benzathine penicillin in a dosage corresponding approximately to 14 mega units in a man weighing 70 kg. Transplant of lymph nodes to 39 other rabbits was carried out 20 to 24 months after inoculation—that is, shortly before treatment—and to 20 other rabbits 32 to 36 months after inoculation—that is, 8 to 12 months after treatment. Of the 39 "pre-treatment receptors", 29 developed syphilitic lesions in which *Treponema pallidum* was demonstrated; of the 20 "post-treatment receptors", none developed syphilitic lesions but one gave a positive response to the T.P.I. test and *Treponema pallidum* was found in the tissues. Two years after treatment the result of the T.P.I. test was still positive in all the original animals. Of 13 rabbits, one untreated and 12 treated, given cortisone 3 years after inoculation, one (which had received treatment) developed characteristic late syphilitic lesions containing *Treponema pallidum*.

It is concluded that if syphilis in the rabbit is allowed to develop for a long period, treatment will not destroy the treponemata, and that it is no doubt the persistence of treponemata which explains the presence of circulating immobilizins. On the other hand, the treponemata appear to have lost much of their virulence for new receptors. The authors have begun a study to ascertain whether *Treponema pallidum* can also be demonstrated in human beings who, in spite of much antisyphilitic treatment, persistently give a positive response to the T.P.I. test.

Robert Lees

1234. **The Action of Penicillin in Late Syphilis: Persistence of *Treponema pallidum* after Treatment. Part II. Human Syphilis.** (Étude de l'action de la pénicilline dans la syphilis tardive: persistance du tréponème pâle après traitement. Seconde partie. La syphilis tardive humaine) P. COLLART, L. J. BOREL, and P. DUREL. *Annales de l'Institut Pasteur* [Ann. Inst. Pasteur] 102, 693-704, June, 1962. 8 figs., 7 refs.

In continuance of their previous paper (see Abstract 1233), the authors now report studies of inguinal lymph nodes derived from 2 human cases of treated latent syphilis, one tabetic insufficiently treated, 5 tabetics treated over several years, and one case of taboparesis treated and studied for 19 years. The lymph-node material was studied by the silver-staining technique already described and also by animal inoculation. Most of the patients had received prolonged treatment with heavy metals and penicillin, and many years had elapsed since the original infection with syphilis. All the patients had persistently positive serological reactions for syphilis. Many of the stained slides showed the presence of typical *Treponema pallidum*; in other instances the organisms were of spiral form but not characteristic morphology. [There are 8 photomicrographs illustrating these organisms.] Rabbits were inoculated with lymph-node material from 4 of the cases. There resulted very tiny lesions which took a long time to appear and which contained typical *T. pallidum*. Sufficient time has not yet elapsed to report on the treponemal immobilization test of the inoculated rabbits. These results do not at present justify clinical or therapeutic conclusions, but indicate the possibility of the survival of virulent *T. pallidum* in syphilitics after a long time and after much treatment.

Robert Lees

Allergy

1235. A Survey of Airborne Pollen in Jerusalem

J. TAS and N. FEINBRUN. *Acta Allergologica* [*Acta allerg. (Kbh.)*] 17, 246-267, 1962. 5 figs., 24 refs.

Two surveys of the pollen in the air were carried out in Jerusalem in 1953-4 and 1955-6. Slides were exposed, a gravity slide method being used. The pollen of grasses is the chief cause of hay-fever in Jerusalem, although *Cynodon dactylon*, the most important grass of the countryside, is rather scarce in Jerusalem. The main season of grass pollen is from April to mid-May, but small quantities are found throughout the year. The pollen of the olive tree is the second most important cause of hay-fever in Jerusalem, but since the olive tree is known to be entomophilous the large amounts of the pollen found on the slides indicated that when it is dry it is carried by the wind. The season is April to mid-June. The three species of *Cupressus* grown near houses produce large amounts of pollen from January to April, but no case of allergy to this pollen has been found. Pine pollen is very abundant in March and one possible cause of sensitivity to it has been observed. Pollens from mulberry trees and from the shrub *Poterium spinosum* in the spring are also not important allergens.

All other plants, including trees, produce very small amounts of pollen. The allergenic species of *Ambrosia* and *Artemisia*, well known in the United States, do not grow in Jerusalem, although *Ambrosia maritima* is common on the coastal plain. *Artemisia* may cause hay-fever in Northern Israel but not in Jerusalem. It is of interest that the pollen-curves for Tel-Aviv, situated on the coast, and for Jerusalem are very similar although the vegetation is quite different.

A. W. Frankland

1236. Controlled Trial of Hypnosis in the Symptomatic Treatment of Asthma

G. P. MAHER-LOUGHNAN, N. MACDONALD, A. A. MASON, and L. FRY. *British Medical Journal* [*Brit. med. J.*] 2, 371-376, Aug. 11, 1962. 1 fig., 10 refs.

In the trial reported here from King's College Hospital, London, one group of asthmatic subjects were treated by hypnosis and a control group with a bronchodilator. The authors worked independently in 3 different hospitals. At each of these, new patients with a history of asthma for at least one year were invited to take part in the trial, unless they had had repeated attacks of bronchitis or were found to have organic disease of the lung. Patients accepted for the trial were kept under observation for one month and then allocated by random selection to "hypnotic" and "control" groups. In each patient the condition was assessed as "mild", "moderate", or "severe", and each was asked to keep a diary in which he noted daily, during the periods of observation and treatment, the presence or absence of attacks of wheezing and asthma and the amount of symptomatic remedy taken. After the month's observation the controls were given a bronchodilator preparation which they had not had before. The hypnosis group were treated by one physician in each of the 3 centres, each using the method to which he was accustomed. The trance achieved was rated as "light", "medium", or "deep". Simple symptom-

removal suggestions were made during hypnosis, which was repeated at intervals of 1, 2, 4, 6, 8, 12, 16, 20, and 24 weeks. In 2 centres an attempt to teach the patient to induce auto-hypnosis was made with some success.

The trial comprised 55 patients (27 in the hypnosis group and 28 in the control group). Multiple precipitating factors were observed in both groups. In the hypnosis group the average number of days per month during which no wheezing took place doubled during the first month and trebled thereafter, whereas there was no appreciable change in the control group. Maximum improvement appears to have been achieved by the third month on the figures given, but it is claimed that of 18 hypnosis patients treated for a further 6 months after termination of the trial 12 became completely free from wheezing. The use of bronchodilator drugs fell progressively in the hypnosis group, but not in the control group. Patients with severe and moderate asthma responded less well than those with severe asthma, and those whose asthma was of less than 20 years' duration better than those whose asthma had been present for over 20 years. Medium and deep trance subjects did better than those who achieved only a light trance. In 2 centres treatment of both groups was undertaken by the same physician, who also assessed the effect of treatment. In the third centre the hypnosis patients were referred to a psychiatrist, but the controls were treated by a physician. The difference between the patients and controls was less striking in this group.

[The assessment of improvement in asthma is notoriously difficult and a double-blind technique is almost impossible to devise when hypnosis is one of the methods of treatment. In this study, as the authors mention, the assessment was purely subjective (reduction of wheezing and use of bronchodilators), and in only one centre was any attempt made to utilize respiratory function tests. Contrary to what the authors say, most patients with asthma of moderate or severe degree show well-marked abnormalities of respiratory function between acute attacks. It may be significant that improvement appears to be related to the duration of treatment, and it is important to note that in no case was dramatic improvement claimed after one or two treatments only. Further observations are necessary, including an assessment of the results of respiratory function tests.]

R. S. Bruce Pearson

1237. Eczema Due to Inhalants

C. A. FRAZIER. *North Carolina Medical Journal* [*N.C. med. J.*] 23, 291-294, July, 1962. 15 refs.

A review is presented of 38 children with atopic dermatitis in whom inhalants were considered to play a prominent part. Of the 38 patients, 20 were worse in winter and gave marked reactions to dust; 6 were worse in the autumn and reacted to ragweed pollen; and 12 were worse in the spring, skin tests revealing sensitivity to tree pollens. Hyposensitization resulted in a complete clearing of the skin in 22 cases and marked improvement in 16. The results with small doses of the antigen were good, but if the dose was of the order given in respiratory allergy an exacerbation of the eczema was likely.

A. W. Frankland

Nutrition and Metabolism

1238. **Nutrition of the Pregnant and Nursing Mother.** (Питание беременной и кормящей грудью матери)
Е. И. КВАТЕР and М. С. МАРŠАК. *Вопросы Охраны Материнства и Детства* [Vop. Okhrany Materin. Dets.] 7, 65-70, June, 1962.

The diet of the expectant and of the nursing mother must be such as to satisfy the physiological needs of both mother and child at all stages of pregnancy and the puerperium. A rational diet will provide the mother with ample quantities of the substances necessary for increase in blood mass, for enlargement of the uterus and mammary glands, for increased function of the vital organs, and, above all, for preventing toxemia of pregnancy and enhancing resistance to infection. The old conception of the limitation of protein intake, especially in toxemia of pregnancy, has now been revised.

The child's weight at 6 months is 25% of its weight at term, so that in the last 100 days of pregnancy, when the rate of foetal growth is greatest, the mother needs extra food, especially proteins, mineral salts, and vitamins. The calorie value of her diet at this stage should be not less than 3,500 C. per day. The minimum amount of protein needed is 120 g., at least half of which should be of animal origin, but extracts such as meat and fish bouillon and soups should be limited in amount, since they tend to overload the liver; the amount of carbohydrate should be relatively smaller than that of protein. Overweight should be avoided by limitation of carbohydrate and animal fats and of foods containing cholesterol, such as eggs, suet, and brain. Sunflower seed and maize oils contain valuable unsaturated fatty acids and should be included in the diet, as should coarse-grained bread. Vitamins A (10,000 to 20,000 units), B₁ (2.5 mg.), B₂ (2.5 to 3.0 mg.), B₆ (15 mg.), B₁₂ (over 3 µg.), C (150 mg.), D (800 i.u.), and E (100 to 150 i.u.) should be provided. The mineral salts for which there is special demand in pregnancy are calcium, potassium, sodium, magnesium, phosphorus, iron, and traces of cobalt and of copper. Common salt should be given liberally in the first half of pregnancy, but limited in the second half, as should the amount of fluid (not over 2 litres per day).

The nursing mother requires a diet of still higher calorie value—4,000 C. per day. It should contain at least 2 g. of protein per kg. body weight, should be rich in calcium and iodine, and contain plenty of milk and milk products. Carbohydrates and fats should be reduced only if the mother is overweight. Fluid, especially milk and fruit juices, should be supplied during each feed.

If toxemia occurs in the early stages of pregnancy, salt should be given, especially if vomiting is severe; meals should be frequent and light, with plenty of protein, extra pyridoxine, and vitamin C; fluid should be drunk between meals and not with them. In the later stages, salt may have to be limited and the total fluid intake restricted to a maximum of 800 ml. per day. The authors recommend eliminating the toxic by-products of disordered metabolism by a series of "unloading days", the diet consisting of fruit juices and compote every 2 hours on the first day, junket and sour

cream every 2½ hours on the second day, and peeled and cored apples 5 times on the third day. In the presence of purpuric eruptions, a course of rutin, 30 mg. twice daily, is recommended. Fats should be curtailed, but proteins are necessary, together with high dosage of vitamins of the group and vitamin C. In the interest of the foetus it is advisable to increase the daily dosage of vitamin B₁₂ to 15 µg. in order to stimulate output of the growth hormone.

L. Firman-Edwards

1239. **Wilson's Disease and the Fanconi Syndrome**
H. G. MORGAN, W. K. STEWART, K. G. LOWE, J. M. STOWERS, and J. H. JOHNSTONE. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 361-384, July, 1962. 12 figs bibliography.

Wilson's disease commonly manifests itself as hepatolenticular degeneration. It has also been known to cause the Fanconi syndrome of multiple renal tubular defects: osteoporosis and fractures have been described, and even cases of rickets. A third case of rickets, the first to precede the neurological signs of Wilson's disease, is here reported from the University of St. Andrews.

The patient, a boy, became mentally and physically retarded from the age of 12, developed osteochondritis dissecans of the knees, and by 17 years had active rickets, with abnormal urinary loss of glucose, calcium, phosphorus, amino acids, and uric acid. Traces of protein were noted intermittently in the urine, which contained a relative excess of ammonium radicals and was poorly acidified. There was no azotaemia. Treatment with citrate and bicarbonate reduced the hypercalciuria but did not help the rickets. Massive dosage of vitamin D₂ (25 mg. or 1 million i.u. a day) cured the rickets in a few weeks. Between the ages of 18 and 20 years the patient developed progressive deterioration of intellect and personality, Jacksonian epilepsy and episodes of stupor and coma, symptoms of extrapyramidal disease, and right hemiparesis. Kayser-Fleischer rings became visible in the corneae. Oral penicillamine therapy led to considerable improvement in the personality and neurological state. Studies of the patient's copper metabolism revealed a low total copper content in the plasma, much reduced caeruloplasmin levels, and virtual absence of plasma oxidase activity.

The parents and brothers of the patient were unaffected clinically and biochemically. The aminoaciduria was virtually unchanged after 3 years' antirachitic and penicillamine therapy. Renal biopsy showed slight, patchy periglomerular and interstitial fibrosis, no calcification, and no evidence of hypokalaemic nephropathy; alkaline phosphatase was present in the normal sites and there was some disorganization of the proximal and distal tubules, with casts in the latter. Dental lesions included enamel hypoplasia, idiopathic apical absorption, and patchy erosion of the lamina dura. Numerous biochemical studies were carried out on the patient.

The authors suggest that the finding of hypercalciuria in the Fanconi syndrome may indicate that Wilson's disease is the underlying cause.

T. B. Begg

Gastroenterology

1240. Eye Signs in Hepatic Cirrhosis

W. H. J. SUMMERSKILL and G. D. MOLNAR. *New England Journal of Medicine* [New Engl. J. Med.] 266, 1244-1248, June 14, 1962. 2 figs., 16 refs.

In a survey carried out among patients at the Mayo Clinic it was found that lid lag (von Graefe's sign) and lid retraction, with or without apparent proptosis, were present in 12% of patients with hepatic cirrhosis compared with only 1% of a control group without evidence of diseases of the eyes, liver, or thyroid gland. Ocular changes were associated with severe impairment of hepatic function, but there was no evidence of thyroid disease. The mechanism of these ocular signs in cirrhosis remains obscure. G. S. Crockett

1241. Hypersideraemia and Excess Iron in the Liver in the Descendants of Subjects with Haemochromatosis. (Hyper-sidérémie et surcharge ferrique hépatique chez les descendants d'hémochromatosiques)

G. SCHAPIRA, J. C. DREYFUS, V. SCHWARZMANN, and J. ÉTÉVÉ. *Revue française d'études cliniques et biologiques* [Rev. franç. Étud. clin. biol.] 7, 485-491, May [received July], 1962. 4 figs., 15 refs.

At the Hôpital des Enfants Malades, Paris, the authors studied 6 descendants of patients with haemochromatosis. All were in good health, but in all 6 the serum iron level was raised, and in 5 the iron content of the liver, as judged from specimens taken for biopsy, was also raised. The one patient who did not have excess liver iron had previously had an episode of anaemia, during which any iron stores present may have been used up. In an addendum the authors state that they have recently seen 2 more cases of the same type. G. S. Crockett

1242. Iron Absorption in Pancreatic Disease

A. E. DAVIS and J. BADENOCH. *Lancet* [Lancet] 2, 6-8, July 7, 1962. 15 refs.

The authors, working at the Radcliffe Infirmary, Oxford, sought to explain the clinical observation that patients with steatorrhoea due to pancreatic disease rarely develop iron-deficiency anaemia. For this purpose they studied iron absorption in normal subjects and patients with idiopathic and pancreatic steatorrhoea by giving a tracer dose of radioactive iron chloride and subsequently measuring the radioactivity of faeces and erythrocytes. The 8 normal subjects studied absorbed 0 to 13% of the ingested iron, the mean value being 6%. Of the 7 patients with idiopathic steatorrhoea studied, 4 absorbed no iron, while the other 3, whose absorption was between 11 and 19%, were all either in remission or under treatment with prednisolone. Of the 14 patients with pancreatic disease studied, iron absorption was within the normal range in 8. In the remaining 6 cases, all of chronic pancreatitis, absorption was increased. In one of these last an absorption of 24% was reduced to 16% by feeding pancreatic extract. These findings were similar to findings in animals, in which ligation of the pancreatic duct or destruction of the exocrine cells of the pancreas with DL-ethionine has been shown to lead to increased iron

absorption and haemosiderosis. The authors suggest that the association of pancreatic damage with increased iron absorption is probably due to failure of the exocrine part of the pancreas to secrete a factor involved in normal iron absorption. G. L. Asherson

1243. Pancreatic Replacement Therapy in Fibrocystic Disease

R. D. HAINES, N. C. HIGHTOWER JR., W. A. CROZIER, and J. M. EIBAND. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 1000-1006, June 23, 1962. 3 figs., 11 refs.

This paper from the Scott and White Clinic and Memorial Hospital and the Scott, Sherwood, and Brindley Foundation, Temple, Texas, describes investigations into the malabsorption state in fibrocystic disease of the pancreas and its treatment with a pancreatic extract, "lipancreatin", in 14 boys and 16 girls ranging in age from 3 to 18 years.

Absorption of fat was determined by the administration of a test meal containing 15 to 20 μ c. of ^{131} I-triolein, after which venous blood samples were collected at intervals of 1 to 2 hours for 6 to 8 hours and faeces for 48 to 72 hours. In normal subjects the peak blood concentration of radioactivity was not less than 10% and the total faecal concentration not more than 5% of the administered dose. The measurement of radioactivity following the test meal in 27 of the children with fibrocystic disease showed a marked degree of lipase insufficiency; in only 2 cases did the radioactivity of the blood reach 10% of the administered dose, while faecal radioactivity was high in all cases. The ^{131} I-triolein test meal was then administered with the addition of 300 to 600 mg. of lipancreatin to 23 of these 27 children. Absorption was very much improved, the mean radioactivity of the blood being 7.3% (compared with 1.7% in the control test) and that of the faeces being 14.2% (compared with 5.75%). Despite the supplement, however, the mean values of radioactivity in the blood and faeces were not entirely normal. Further tests showed that absorption of ^{131} I-triolein was more effective with the supplement of 300 to 600 mg. of lipancreatin than with a supplement of 300 to 900 mg. of quadruple-strength pancreatin ("viokase"), while tests with a supplement of enteric-coated tablets of triple-strength pancreatin (975 mg.) showed very little improvement of absorption.

Lipancreatin in a dosage of 300 to 500 mg. 3 times daily was given to 24 children with fibrocystic disease for 6 to 24 months. In all cases a marked decrease in the daily number of stools was noted, and in some cases this improvement was very striking. The patients also gained in weight and height, the gains being comparable to those to be expected in a group of normal children of the same age and sex. No adverse effects were observed. The ^{131} I-triolein test meal with lipancreatin supplement was again administered to 12 patients after they had been receiving lipancreatin maintenance therapy for 3 to 6 months; a further improvement in absorption, as compared with that indicated by the previous lipancreatin test, was found in 8 cases.

The authors conclude that lipancreatin is a valuable adjunct to the treatment of fibrocystic disease of the pancreas.

Joseph Parness.

INTESTINES

1244. Enteropathy and Protein Loss. (Entéropathies et déperdition de protéines)

H.-P. WITSCHI, S. BARÁNDUN, and D. NUSSLÉ. *Gastroenterologia* [*Gastroenterologia* (Basel)] 98, 65-75, 1962. 5 figs., 19 refs.

The authors, working at the University of Berne, have studied the role of the gastro-intestinal tract in hypoproteinaemia. They recall that the serum level of protein and, in particular, that of albumin may be lowered in gastro-intestinal disease and that this is usually attributed to poor absorption of amino acids or to loss of protein in inflammatory exudate or blood. After establishing normal values for Gordon's ^{131}I -polyvinylpyrrolidone (PVP) test in children (up to 1% of the injected dose eliminated in the stools) and in adults (up to 0.65%), they determined the faecal elimination of ^{131}I -PVP in a number of pathological conditions. Elimination was increased in Hirschsprung's disease, coeliac disease, congenital jejunal stenosis, hypertrophic gastritis, regional ileitis, sprue, and ulcerative colitis; also in lymphosarcoma and tuberculosis of the bowel, in constrictive pericarditis, and in nephrosis. In nephrosis this gastro-intestinal loss of protein may be the reason for hypoproteinaemia which cannot be attributed to proteinuria alone, and may also explain the raised protein catabolism seen in the acute phase of the nephrotic syndrome in children.

The albumin and various globulin fractions demonstrated, by the Ouchterlony plate technique, to be present in the contents of the small intestine of normal subjects were found to be increased in disease. In one case γ -globulin isolated from the gastro-intestinal tract had a sedimentation constant of 6 to 7 Svedberg. Proteins with a molecular weight in the serum of about 1,000,000 were also found. This excessive passage of protein into the gastro-intestinal tract may lead to increased aminoaciduria, since the protein is broken down to amino acids in the bowel. It seems likely that in these cases the body synthesizes protein at a maximum rate and that there is thus no firm rationale for prescribing high-protein diets or protein hydrolysates. The authors conclude that the ^{131}I -PVP test together with intubation is of value in the investigation of hypoproteinaemia and in the location of gastro-intestinal lesions accompanying that condition.

G. L. Asherson

1245. Surgical Aspects of Enteropathy with Protein Loss. (Aspects chirurgicaux des entéropathies avec déperdition de protéines)

M. BETTEX, D. NUSSLÉ, and L. ECKMANN. *Gastroenterologia* [*Gastroenterologia* (Basel)] 98, 76-86, 1962. 5 figs., 19 refs.

In this paper from the University of Berne the authors describe the hypoproteinaemia, sometimes severe enough to cause generalized oedema, which may occur in surgical disorders of the gastro-intestinal tract, such as chronic partial obstruction and chronic volvulus and intussusception. They describe a case in which generalized oedema and hypo-

proteinaemia were the presenting features. There were no bowel symptoms. The results of the radioactive polyvinylpyrrolidone test and the x-ray appearances of the intestinal mucosa were abnormal. At operation the bowel was thickened and pigmented and the lymphatics were dilated. Histologically, lymphatic stasis, inflammatory infiltration of the mucosa, and pigmentation of the muscle were seen.

This case illustrates one of the lesions which may underlie "essential" hypoproteinaemia. The authors conclude that some cases of "essential" hypoproteinaemia can be cured by surgery, and that it may not be possible to relieve the oedema by medical treatment before operation.

G. L. Asherson

1246. Gastrointestinal Arterial Insufficiency—Abdominal Angina

P. S. BENTLIF, G. E. BURKE, J. R. KELSEY, and E. S. CRAWFORD. *Southern Medical Journal* [*Sth. med. J.* (B'ham, Ala.)] 55, 573-576, June, 1962. 9 refs.

This paper from Baylor University College of Medicine, Houston, Texas, describes a study of 8 patients with suspected or proven "abdominal angina"—atherosclerosis of the mesenteric arteries leading to post-prandial pain and loss of weight. The authors state that in their view the classic symptoms do not occur in every case and that it is easy to overlook the time relationship between pain and food ingestion. Since the interval between pain and eating may vary from 30 minutes to 3 hours, there may be confusion with an ulcer-type pain; there is also a risk of mistaking the condition for chronic pancreatitis.

In 4 of the 8 patients the clinical suspicion of mesenteric insufficiency was confirmed by the finding of a pressure gradient at operation; in 2 patients suggestive symptoms were not associated with demonstrable stenosis, while in another 2 patients stenosis was found though the symptoms were atypical. An abdominal bruit was heard in 5 of the 6 cases in which stenosis was confirmed at operation. Tests for splanchnic blood-flow, tests of fat absorption, and jejunal biopsy were not helpful in diagnosis and, although aortography is useful, the authors consider that the diagnosis "remains clinical".

D. A. K. Black

1247. The Effect of Certain Hormonal Preparations on the Absorption of Fatty Acid by the Small Intestine. (О влиянии некоторых гормональных препаратов на всасывание жирных кислот в тонком кишечнике)

N. V. ANASTAS'eva. *Проблемы Эндокринологии и Гормонотерапии* [*Probl. Endokr. Gormonoter.*] 8, 53-59; July-Aug., 1962. 2 figs., 12 refs.

The effects of certain hormones on the absorption of fatty acid by the small intestine were studied on the isolated intestinal loop, prepared by the technique of Thiery and Pavlov, of the dog. Every 30 minutes, 15 ml. of an emulsion of oleic acid, bile, and pancreatic juice (or an appropriate quantity of 4% butter emulsion) was introduced into the loop. Fluid was withdrawn, also at 30-minute intervals, and its fatty acid content estimated. At 1½ hours after the beginning of the experiment the animals were given injections of the following hormone preparations: posterior lobe of the pituitary ("pituirin"), 3 units subcutaneously; adrenocorticotrophic hormone (ACTH), 1 unit per kg. body weight, intramuscularly; thyroxine, 0.0005 mg. intravenously; insulin, 0.75 unit per kg. subcutaneously; suprarenal

cortex ("cortin"); 1 unit per kg., intramuscularly; and adrenaline, 0.08 ml. of a 0.1% solution per kg., subcutaneously. The duration of each experiment was 3½ hours. Pituitrin lowered the absorption of fatty acids; ACTH and cortin increased it. Thyroxine caused a transitory rise, but in 30 minutes absorption was normal. Adrenaline caused a slight fall in the rate of absorption, but insulin had no definite effect.

L. Firman-Edwards.

1248. **Röntgenographic Signs Produced by *Taenia saginata***
L. S. MONROE and R. A. NORTON. *American Journal of Digestive Diseases* [Amer. J. dig. Dis.] 7, 519-522, June, 1962. 3 figs., 5 refs.

The authors, giving illustrated examples, describe how barium-meal examination of the small bowel may assist in the diagnosis of beef tapeworm infestation. This worm averages 12 to 15 feet (3.6 to 4.6 m.) in length; its scolex is usually attached in the mid-portion of the small intestine and its anterior end is extremely narrow. It appears on the radiograph as a long, thread-like radiolucency, tapering gradually and lying within the column of barium in the ileum.

When *Taenia saginata* is folded upon itself a double area of radiolucency may be produced separated by a short, irregular opacity, an appearance which may suggest a diagnosis of ascariasis. Tangled masses of *Ascaris* can occasionally be seen without the use of contrast medium, but with barium the parasite is sharply outlined; it is of uniform width except at its ends and is short compared with *Taenia*. The worm's intestinal tract shows up as a filamentous smooth radio-opacity.

Eirian Williams

1249. **A Study of Ulcerative Colitis in New Zealand, Showing a Low Incidence in Maoris**

R. D. WIGLEY and B. P. MACLAURIN. *British Medical Journal* [Brit. med. J.] 2, 228-231, July 28, 1962. 29 refs.

New Zealand is a relatively closed community in which it is estimated that at least 80% of hospital patients are treated in public hospitals, where the "International Classification of Disease" is used universally for the coding of discharge diagnoses in the records. A study of such records derived from hospitals serving the southern part of the North Island, an area whose population is 464,000, revealed that during the 5-year period 1954-8 the incidence of ulcerative colitis severe enough to warrant admission to hospital was about 5 to 6 new cases per 100,000 per annum, with a mortality of 0.9 per 100,000. The incidence of colitis not requiring hospital treatment was not determined. There was no over-all sex difference, but males predominated up to the age of 20 and females thereafter. Males appeared to suffer a milder form of the disease with a lower death rate. The incidence in towns, where hygiene is better than in rural areas, was nearly double the rural incidence. This finding and the infrequent involvement of both husband and wife were considered to provide evidence against an infective cause. The family incidence of the disease appeared to be greater than could be attributed to chance, but further study of this aspect is required.

There were no Maoris among the patients with ulcerative colitis in this area, and an analysis of hospital records for the whole of New Zealand for the same 5-year period revealed only 2 definite cases in Maoris (total hospital intake 137,152), with no deaths, compared with over 600 cases in Europeans

(total intake 2,036,911). Available evidence suggests that this apparent difference in incidence of ulcerative colitis between the two racial groups is a genuine one.

A. Gordon Beckett

1250. **The Irritable Colon Syndrome: a Study of the Clinical Features, Predisposing Causes, and Prognosis in 130 Cases**
N. A. CHAUDHARY and S. C. TRUELOVE. *Quarterly Journal of Medicine* [Quart. J. Med.] 31, 307-322, July, 1962. 2 figs., 20 refs.

Colonic pain, disordered bowel habits, and the passage of mucus per rectum were the main findings in 130 patients with the irritable bowel syndrome studied at the Radcliffe Infirmary, Oxford. Painless diarrhoea occurred in only 24 cases, spastic colon (that is, with colicky or continuous pain over the colon or lower abdomen) being present in all the remaining 106 cases, in half of which the pain was relieved by defaecation. The series contained twice as many women as men. Most of the patients were aged 20 to 60 years, the maximum incidence being in the age groups 40 to 49 for men and 20 to 49 for women.

Bowel action was variable. The symptoms were exacerbated in 54 cases by certain foods, particularly fresh fruit and fried foods. Most patients had general symptoms such as fatigue and depression. Purgatives were taken regularly by 29 patients and occasionally by 10. In 34 cases the symptoms dated from an attack of infective dysentery. Psychological features, such as anxiety or worry over trifles, were present in 77% of cases in the spastic colon group and 87.5% of those in the painless diarrhoea group. Most patients were in good physical condition, but 60% had tenderness over one or more parts of the colon. Sigmoidoscopy revealed in every case abnormal motility of the colon, hyperaemia of the mucosa, and excessive mucus secretion. Colonic biopsy was carried out in a number of cases and showed a normal mucosa.

About one-third of the patients lost their symptoms with simple therapy, which included reassurance and the administration of sedatives, bulk-providers, and, where necessary, codeine phosphate. Most of the others were improved on this regimen, improvement taking place mainly in the first few months and being greatest in patients with a past history of dysentery. The prognosis was worse where identifiable psychological factors were present.

M. Lubran

1251. **Nephrolithiasis as a Complication of Ulcerative Colitis and Regional Enteritis**

J. J. DEREN, J. G. PORUSH, M. F. LEVITT, and M. T. KHLNANI. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 843-853, June, 1962. Bibliography.

The incidence of renal calculi was studied in 583 patients with ulcerative colitis or regional ileitis treated at Mount Sinai Hospital, New York, between 1950 and 1960 and possible predisposing factors were assessed. No attempt was made to prove the apparent increased frequency of nephrolithiasis in these diseases.

Stones were found in 11 (3.2%) of the 344 patients with ulcerative colitis, in 14 (6.3%) of the 221 with regional ileitis, and in 3 (16.7%) of the 18 with ileocolitis. Of the 28 patients with stones, 20 were males. The interval between the onset of the illness and the discovery of stones ranged from 1 to 33 years, the average being 10 years. The stones were judged or proved to be uric acid stones in 13

cases and calcium stones in 9; in 6 they were unclassified. Stones were present in 23 (6.7%) of the 342 patients who had undergone excisional or short-circuiting operations, and in 12 (7.4%) of the 163 who had undergone ileostomy, compared with only 5 (2.1%) of those who had not been operated on. Urinary infection was present at some stage of the disease in 9 patients with uric acid stones and in 5 with calcium stones. No significant elevation of serum urea, calcium, phosphorus, or uric acid levels was found in any of the patients with stones, but there was a reduced serum potassium level in many cases. In the majority, the urine had a consistently acid reaction, although precise pH measurements were not carried out. A conspicuous feature in most cases was a diminished urinary volume. Although the degree of this oliguria was difficult to measure, it was reflected in the high specific gravity of casual specimens of urine (1.025 or more in 13 of the 28 cases). Symptoms due to stones developed in the postoperative period in 4 cases and in the post-partum period in one. It is pointed out that whereas in 59% of these cases the stones were formed of uric acid, in general only 5 to 15% of all renal calculi are of this composition.

The probable mechanisms are discussed, the most important of which is considered to be the low volume of urine resulting from the inordinate loss of fluid through the gastrointestinal tract, either transiently during an exacerbation of the disease or chronically owing to a diminished absorptive surface, unless compensated by increased intake. Further loss of absorptive surface follows surgery, particularly ileostomy, before this becomes regulated. The need for adequate replacement of fluid, especially after operation, is stressed. The increased loss of alkaline faecal material, including potassium, causes systemic acidosis, leading to a persistently acid urine which predisposes to the formation of uric acid stones. Reduction of glomerular filtration rate and potassium deficiency may also play some part in the formation of these stones, as may the loss of the "salting-in" effect of various solutes lost from the gastrointestinal tract. The formation of calcium phosphate stones on the other hand becomes more likely if the urinary pH rises as a result of the action of urea-splitting organisms present in pyelonephritis, to which patients with ulcerative colitis have an increased susceptibility. This is seen particularly in the presence of colostomy and ileostomy and is not due simply to frequent catheterization. There is no evidence that obstruction of the renal tract or increased excretion of uric acid or of calcium plays a significant part in the causation of nephrolithiasis in these conditions. *A. Gordon Beckett*

1252. Experience with Short and Long Term Courses of Local Adrenal Steroid Therapy for Ulcerative Colitis: Report of 98 Cases

J. A. SPENCER and J. B. KIRSNER. *Gastroenterology* [*Gastroenterology*] 42, 669-677, June, 1962. 17 refs.

At the University of Chicago Clinics 98 cases of ulcerative colitis given local treatment with corticosteroid drugs over a period of 4 years were analysed. The double-blind technique was not used. Good initial improvement was obtained in 72 cases. This was less frequent in cases with proctoscopic evidence of severe activity (45%) than in those with moderate or mild activity (80%), and in cases in which disease involved the whole colon (54%) than in those with disease limited to the descending colon (76%). The presence of chronic changes or the duration of the disease did not

affect the result. While the clinical response was usually maximal after 2 days, the improvement in the proctoscopic appearances did not reach its maximum until after 2 weeks. In only one-third of the patients who became clinically well did the mucosa become normal, although friability of the mucosa disappeared in 69%. In 13 cases the rectal mucosa did not change, but the clinical response was favourable. Conversely, in 3 the mucosa healed to a mild erythema only, although the diarrhoea persisted. Return of normal histology was not demonstrated.

Of the 72 patients who responded well, the total relapse rate was 70% in the 43 whose treatment was stopped within 6 months compared with 48% in the 29 who continued treatment for more than 6 months. Of the latter, relapse occurred in 7 during treatment, and in another 7 after treatment had been stopped. The remainder continued in remission, 10 still having therapy. In other words, 44 (62%) of the patients with a good initial response suffered a relapse, and of these 30 had treatment for less than 6 months; 28 remained in remission, and of these 13 had treatment for less than 6 months. Of the 15 who suffered relapse during treatment, 9 were given bigger doses and 4 of the 9 improved. Of the 29 who suffered relapse after the enemas were discontinued, 24 had further treatment, 14 having a good response. Of the 8 patients who had a relapse after a second course of enemas 5 responded to a third course.

None of the corticosteroid drugs used appeared to have any advantage over the others. Although the highest level reached by the enemas appeared to be the sigmoid, increasing the volume of fluid above 30 ml. did not improve the results. Antispasmodics were not used. Of the patients in whom the response was good, 10 had previously failed to improve with corticosteroid drugs administered systemically. The addition of local to systemic corticosteroid therapy in 7 cases seemed to convert an incomplete response to a complete and satisfactory one. The side-effects of corticosteroids were seldom encountered. Fluid retention occurred in 5 patients, 4 of whom were having hydrocortisone hemisuccinate. In 2 patients receiving hydrocortisone acne developed; 2 developed arthralgia concurrently with exacerbation of diarrhoea within a week after spontaneous abrupt discontinuance of the corticosteroid enemas. Except for these 2, sudden cessation of the enemas caused no adverse reactions. In 16 patients with various conditions made worse by systemic corticosteroids there was no reactivation of these disorders.

A hyperplastic type of mucosal healing occurred in some patients, pseudo-polyps occasionally developing rapidly and reaching a large size. Multiple pseudo-polyps were seen in 15 of the 83 patients in whom proctoscopy was performed after rectal treatment with corticosteroids. In 6 of these the polyps had been present before treatment and continued to grow during treatment. The long-term therapy originally planned proved to be impossible in many cases on account of its inconvenience, but, in the event, it appeared to have no appreciable advantage over short-term therapy. The good results may have been due to absorption of small amounts of corticosteroid, or to healing of one area facilitating healing of the mucosa of the entire colon, or to improvement of the rectal mucosa decreasing the desire to defaecate.

The authors conclude that "complete remissions of ulcerative colitis are accomplished and sustained less frequently with the use of adrenal steroid enemas than with systemic steroid therapy". *A. Gordon Beckett*

Cardiovascular System

1253. Recent Experience with Pericarditis with Special Reference to Idiopathic Pericarditis

S. R. NEMSER and E. DONOSO. *Journal of the Mount Sinai Hospital [J. Mt Sinai Hosp.]* 29, 229-238, May-June, 1962. 28 refs.

The authors review all cases of pericarditis seen at the Mount Sinai Hospital, New York, during the years 1958 and 1959, with the exception of cases secondary to thoracic surgery or myocardial infarction. Of the 39 patients studied, 21 were male and 18 female. In 19 the pericarditis was idiopathic, in 4 it was neoplastic in origin, in 3 rheumatic, in 3 myxoedematous, and in 2 uraemic; there was only one case of purulent pericarditis. Of the 19 patients with acute idiopathic pericarditis (average age 41.9 years), 12 were male and 7 female. In 18 there was a clear history of a preceding respiratory-tract infection, and cough and chest pain were the prominent symptoms. A pericardial friction rub was heard at some time in the clinical course of the disease in 11 of the 19 cases and was often transient. An associated pneumonitis was found in 6 cases, and left-sided pleural effusion occurred in 8. Of 18 patients examined radiologically the cardiac outline was enlarged in 13; this was thought to be due to pericardial effusion and not to cardiac dilatation. Cardiac tamponade was rare, although in all patients some evidence of cardiac compression, varying from pulsus paradoxus to a raised venous pressure and an enlarged liver, was present. In the 4 cases in which pericardiocentesis was performed the effusion was serous or serosanguineous. The electrocardiogram was abnormal in 17 patients, the most characteristic finding being changes in the ST segment with or without changes in the T waves. A polymorphonuclear leucocytosis was common, together with a raised erythrocyte sedimentation rate. In 4 cases the antistreptolysin-O titre was raised. Of the 15 patients in whom a tuberculin test with purified protein derivative was performed, the result was positive in 10. Symptoms responded promptly in patients treated with corticosteroid drugs, but in those treated with salicylates, and in those not treated, the disease ran a prolonged course. The small size of each therapeutic group makes final evaluation of therapy difficult, but the authors are sufficiently impressed by the response to corticosteroid therapy to recommend this as the treatment of choice.

J. Warwick Buckler

1254. Mycotic Aneurysm. (Aneurisma micotico)

S. ZAJARIAS, R. CONTRERAS, and F. BERMÚDEZ. *Archivos del Instituto de cardiología de México [Arch. Inst. Cardiol. Méx.]* 32, 11-26, Jan.-Feb. [received July], 1962. 9 figs., 7 refs.

In an analysis of 2,500 consecutive necropsies performed at the National Institute of Cardiology, Mexico, the authors found 188 cases of bacterial endocarditis, 12 with mycotic aneurysm. The ages of the patients at death ranged from 2 to 32 years. Congenital heart lesions were present in 4 (coarctation of the aorta in 2, interventricular septal defect in one, and congenital mitral stenosis in one), 5 had rheumatic carditis, and in 3 no disease preceding the endocarditis

was discovered. In 8 of the cases the aneurysm was due to embolism, while in the others it was due to infection. There was complete thrombosis in 4 of the aneurysms and partial thrombosis in one. Rupture occurred in one case only.

Mycotic aneurysms are difficult to diagnose because they are usually small and silent. Only those large enough to be felt or which cause painful symptoms are easily recognized. In this series only 2 were diagnosed during life. One of these progressed towards rupture; the other produced ischaemia in the legs due to thrombosis at the aortic bifurcation. The prognosis in these cases is poor, but the arrest of bacterial endocarditis by antibiotics will now make more cases of aneurysm amenable to surgical treatment. The authors suggest that precordial pain in bacterial endocarditis should lead to suspicion of thrombosed mycotic aneurysm.

D. Goldman

1255. Late Followup of 64 Patients with Subacute Bacterial Endocarditis Treated with Penicillin

P. BUNN and J. LUNN. *American Journal of the Medical Sciences [Amer. J. med. Sci.]* 243, 549-557, May, 1962. 8 refs.

The results of a long-term follow-up of 59 patients who had been treated with penicillin for subacute streptococcal endocarditis are described in this paper from the State University of New York Upstate Medical Center, Syracuse. (Not included in the study were 5 additional patients, similarly treated, who were lost to follow-up but were known to be fit on discharge from hospital.) The original treatment had consisted in systemic administration of penicillin for an average of 33 days in a dosage of 5 to 12 million units daily. In 21 cases 1 g. of streptomycin was also given every 24 hours.

The patients were followed up until death or for a minimum of 5 years. At 5 years 36 patients were still alive; 28 of them survived for 6 to 13 years. Despite underlying heart disease, 33 patients were sufficiently well to follow their employment. Altogether 31 patients died, 8 of them more than 5 years after discharge from hospital. The chief causes of death were congestive cardiac failure and ruptured aortic valve. There were relapses in 6 of the original patients, and these relapses were caused by a streptococcus apparently identical with that associated with the first infection. In 4 of the 6 the initial course of treatment had been of less than 3 weeks' duration; all 6 were successfully re-treated.

The authors state that unfavourable prognostic indications are aortic valve endocarditis and the age of the patient. In their opinion the prognosis is poorest in elderly patients with arteriosclerotic aortic valves, especially if congestive cardiac failure co-exists with the bacterial infection. Once the infection is overcome there is no evidence that the life of the patient is shortened in any way by the previous infection. The 100% mortality rate before 1944 is recalled and an appeal made for earlier diagnosis of this condition.

J. Warwick Buckler

1256. Thromboembolic Complications in Connection with Mitral Commissurotomy after Discontinuation of Anticoagulant Therapy

S. DAHLGREN and V. O. BJÖRK. *Journal of Thoracic and Cardiovascular Surgery* [*J. thorac. cardiovasc. Surg.*] **43**, 780-784, June, 1962. 1 fig., 16 refs.

Long-term anticoagulant therapy is often given to patients with mitral stenosis in order to reduce the frequency of embolism. The management of such patients after operation is controversial. In 1958-9 37 patients with mitral stenosis underwent commissurotomy at University Hospital, Uppsala. Of these, 32 had not received long-term anticoagulant therapy and embolization in connexion with the operation developed in one only. On the other hand, of 5 patients receiving anticoagulant therapy which was discontinued immediately before operation, thromboembolic complications developed in 4, 2 of whom died. In one of the fatal cases the emboli were in the brain and left kidney, and in the other they were in the left carotid, superior mesenteric, splenic, and iliac arteries. Of the other 2 patients in this group who had embolic incidents, one required an embolectomy from the left leg and the other from the left arm.

It is concluded that anticoagulant therapy should not be abruptly withdrawn in these cases and that heparin should be substituted 2 days before the operation and continued over the operative and postoperative period. Some workers have found that dicoumarol (or its equivalent) can be continued during operation "without risk of prohibitive haemorrhage".

Andrew M. Desmond

1257. Atrial Tachycardia with Block Treated with Digitalis

W. L. MORGAN and G. M. BRENNAN. *Circulation* [*Circulation*] **25**, 787-797, May, 1962. 4 figs., 20 refs.

Atrial tachycardia and atrial flutter are both commonly accompanied by atrioventricular block of 2:1, 3:1, or 4:1, but the former is characterized by a lower atrial rate (under 250 per minute) and the presence of an isoelectric portion of base-line between the atrial complexes. Recently some workers have suggested that atrial tachycardia is most often due to digitalis intoxication, in which case the correct treatment is withdrawal of the drug and administration of potassium salts, which will usually restore sinus rhythm.

In this paper from Henry Ford Hospital, Detroit, the authors describe 15 cases of atrial tachycardia with block, in only 6 of which was digitalis causing the arrhythmia. In all 6 there was a sinus rhythm on withdrawal of digitalis. In the remaining 9 cessation of digitalis administration had no effect, and the drug was started again with benefit; this was followed by slowing of the heart rate, due to an increased degree of block or to restoration of sinus rhythm in 7. One of the 9 patients who had no detectable heart disease had had recurrent attacks of tachycardia since childhood and a sustained tachycardia for 5 years; the tachycardia persisted in spite of digitalis. All except 2 of the 15 patients were over 50 years of age; 5 had rheumatic heart disease and 6 had coronary disease.

J. A. Cosh

1258. Potassium Supplements and Congestive Heart Failure

C. T. G. FLEAR and R. H. CAWLEY. *British Heart Journal* [*Brit. Heart J.*] **24**, 337-348, May, 1962. 33 refs.

At the Queen Elizabeth Hospital, Birmingham, potassium supplements were given in the treatment of congestive cardiac failure in a total of "397 consecutive admissions of 272

patients". Potassium salts equivalent to 30 mEq. or more of potassium a day were given by mouth for at least 7 days to 125 patients, of whom 49 had had an initial control period of one to 3 weeks. Serial serum electrolyte values were estimated before, during, and after therapy and in all 397 admissions the patients received digitalis and a mercurial diuretic intramuscularly 3 times a week, provided they were not uraemic. The authors admit that the episodes in which potassium was administered were clinically more severe at the time this treatment was instituted than those in which it was not prescribed. Statistically significant correlations between clinical improvement and a rise in the serum sodium level or between deterioration and a fall were found in patients with or without hyponatraemia on admission. Potassium supplements were found to be effective in preventing a fall in the serum sodium level, or in bringing about an increase, only in those cases in which there was hyponatraemia initially. Changes in the serum potassium concentration were less clear-cut, since rises and falls occurred with the same frequency as in the control groups. The rises in the serum potassium level were never dangerous and were unrelated to the dose of potassium administered.

The authors consider that the risks attendant upon the administration of potassium supplements by mouth are slight and possibly unrelated to consequent changes in serum potassium levels. They initiated this study in the hope of ascertaining which patients, if any, would benefit from potassium supplements, how they may be distinguished clinically on admission, and how their prognosis would be ultimately altered. The authors conclude, however, that these characteristics cannot be precisely defined in congestive heart failure, although there was some evidence that female patients, or patients with congestive cardiac failure of non-rheumatic aetiology, responded more favourably to potassium salts than any other group. A higher proportion of patients with rheumatic heart disease and of male patients gave a history of exertional dyspnoea of more than 5 years' duration.

It is considered that these results are only provisional and approximate, and that more comprehensive methods of observation and measurement of clinical and biochemical variables, together with adequate control periods, are required before the precise indications for inclusion of potassium supplements in the treatment of congestive heart failure can be determined.

J. Warwick Buckler

1259. Patterns of Human Myocardial Oxygen Extraction During Rest and Exercise

J. V. MESSER, R. J. WAGMAN, H. J. LEVINE, W. A. NEILL, N. KRASNOW, and R. GORLIN. *Journal of Clinical Investigation* [*J. clin. Invest.*] **41**, 725-742, April, 1962. 9 figs., 34 refs.

Myocardial oxygen extraction has been studied by the technic of coronary venous catheterization and measurement of multiple coronary arteriovenous oxygen differences. One hundred and ten observations were made at rest and 80 during exercise.

During rest the control subjects had a normal frequency distribution of myocardial oxygen extraction percentages and coronary venous oxygen saturations, averaging 70 and 29%, respectively. Resting values remained essentially constant throughout exercise and rest postexercise periods. Subjects with coronary insufficiency had a lower mean

myocardial oxygen extraction and a higher mean coronary venous oxygen saturation than did the controls at rest. During exercise myocardial oxygen extraction percentage increased and coronary venous oxygen saturation decreased significantly in 82% of the subjects. In congestive heart failure and in critical mitral stenosis, resting myocardial oxygen extraction percentage was increased when effective cardiac output was less than 3.0 l. per minute per m². During exercise the pattern of myocardial oxygen extraction appeared to be governed by the presence or absence of co-existing coronary insufficiency.—[Authors' summary.]

DIAGNOSTIC METHODS

1260. The Electrocardiographic Sign of Acute Hemopericardium

R. E. LONDON and S. B. LONDON. *Circulation* [Circulation] 25, 780-786, May, 1962. 8 figs., 3 refs.

Acute haemopericardium may cause an increase in the height of T waves in precordial leads, sometimes to over 10 mm., or it may cause an initially negative T wave to become positive. This pattern was observed in the electrocardiogram in 8 patients at the Mount Sinai Hospital of Greater Miami, Florida, who subsequently came to necropsy. In 5 cases the aorta had ruptured into the pericardium (due to medionecrosis of the aorta in 4 and to rupture of an aneurysm of a sinus of Valsalva in one). In the remaining 3 cases cardiac rupture followed infarction.

In 5 of the 8 cases the T waves were narrow and pointed, recalling the effect of a raised serum potassium level on the heart. It is suggested that the tall T waves are, in fact, due to release of potassium from the erythrocytes shed into the pericardium.

J. A. Cosh

1261. Electrocardiographic Findings in 122,043 Individuals

R. G. HISS and L. E. LAMB. *Circulation* [Circulation] 25, 947-961, June, 1962. 16 refs.

An analysis is presented of the electrocardiographic findings in 122,043 healthy males, aged between 16 and 50 years, who were established flying personnel or were entering upon a course of training for flying duties.

The largest number of "abnormalities" found were disturbances of rhythm, the chief of which, expressed as rate per 1,000 subjects, were ventricular premature systoles, 7.8; atrial rhythm (high nodal), 5.5; atrial premature systoles, 4.3; and nodal rhythm, 2.1. Virtually all the subjects had normal hearts.

Conduction disturbances included first-degree atrioventricular block, 6.5 per 1,000; Wolff-Parkinson-White syndrome, 1.5 per 1,000; and right bundle-branch block, 1.8 per 1,000. None of these conditions showed any tendency to increase with the age of the subject, although this was observed in the few cases of left bundle-branch block, 13 of the 17 patients being over 35 years of age, indicating causation by acquired heart disease. The importance of vagal tone in the healthy heart was indicated by the 96 cases of atrioventricular dissociation with nodal or ventricular escape; in all the subjects this was transitory and abolished by exercise.

Non-specific T-wave changes were common (11.5 per 1,000), and were most frequently the presence of low T waves, 2 mm. or less, in limb and/or chest leads. The

majority of these subjects appeared normal although a few had evidence of ischaemic heart disease. Myocardial infarction patterns were found in 42 subjects, most of whom were over 30 years of age and few of whom had any clinical signs or history suggestive of infarction.

J. A. Cosh

1262. Myocardial Transit Time: a New Technic for Evaluating Coronary Circulation. I. Effect of Systemic Blood Pressure

H. BERNSTEIN, R. B. T. SKELTON, H. GOLD, D. W. IRVING, and E. CORDAY. *American Journal of Cardiology* [Amer. J. Cardiol.] 9, 777-782, May, 1962. 7 figs., 9 refs.

The authors, at the University of California School of Medicine, Los Angeles, have studied the speed of transmission of hydrogen-labelled blood through the myocardium in 17 mongrel dogs. Two hydrogen-sensitive electrodes were prepared and placed in the heart—one at the base of the aorta by means of retrograde catheterization through a carotid artery; the other into the coronary sinus through an incision in the auricular appendage. The signals from these electrodes and the mean arterial pressure were monitored with an oscilloscopic polygraph. Hydrogen gas was passed into the endotracheal tube through a closed system. The myocardial transit time was calculated as the interval between the onset of the deflection of the tracing of the signals from the electrode in the aorta and the onset of the deflection of the tracing of the signals from the electrode in the coronary sinus.

The average myocardial transit time ranged from 3.2 to 8.2 seconds, with a mean of 5.2 ± 1.0 seconds. In those dogs in which the arterial pressure was relatively stable the myocardial transit time was reproducible with considerable accuracy.

The arterial blood pressure was raised either by applying an aortic snare or by the infusion of noradrenaline. The myocardial transit time was found to vary inversely with the arterial blood pressure; in one experiment the transit time fell from about 6 seconds at 60 mm. Hg to about 2 seconds at 115 mm. Hg. During haemorrhagic hypotension the myocardial transit time was markedly prolonged.

The results demonstrate a reproducible method for determining the rate of transfer of hydrogen from the coronary ostia to the coronary sinus. The method has the advantage that it does not require the direct injection of any tracer material into, or any operative manipulation of, the coronary arteries. The significance of the myocardial transit time determined with hydrogen-sensitive electrodes has not been fully established, but it seems probable that it reflects coronary blood flow. The authors are now studying the effects of other variables on the myocardial transit time determined in this manner.

G. Clayton

1263. The Relative Efficiencies of Some Serum-enzyme Tests in the Diagnosis of Myocardial Infarction

B. A. ELLIOTT and J. H. WILKINSON. *Lancet* [Lancet] 2, 71-72, July 14, 1962. 2 figs., 18 refs.

Because heart muscle is relatively rich in glutamic-oxalacetic transaminase, lactate dehydrogenase, aldolase, and other enzymes, studies of the serum enzyme levels have been extensively used in support of the diagnosis of myocardial infarction, especially when electrocardiographic evidence is inconclusive.

In the past the most widely used enzyme test has been the serum L-aspartate : 2-oxoglutarate amino-transferase, formerly known as serum glutamic-oxalacetic transaminase (S.G.O.T.) and first introduced by LaDue *et al.* in 1954. The value of this test has been substantiated by numerous favourable reports; but the test has the disadvantage that the rise in S.G.O.T. level is transient, and that values within the normal range may well be observed if blood is not collected for enzyme assay within 24 to 36 hours of the onset of symptoms. In view of this drawback, some investigators have preferred to use serum lactate dehydrogenase (S.L.D.), the level of which remains high for longer than that of S.G.O.T. (Wacker *et al.* (*New Engl. J. Med.*, 1956, 255, 449) and White (*New Engl. J. Med.*, 1956, 255, 984; *Abstr. Wild Med.*, 1957, 22, 164)). Unfortunately, the tissue specificity of the S.L.D. is relatively low, and raised values may sometimes be misinterpreted. In an attempt to improve the specificity of this test, the authors recently carried out electrophoretic studies which showed that serum α -hydroxybutyrate dehydrogenase (S.H.B.D.) activity is principally associated with the fast-moving L.D. isoenzymes characteristic of heart muscle. The finding of normal S.G.O.T. activity does not exclude a diagnosis of myocardial infarction, and it is common experience that the longer the interval between the clinical episode and the first enzyme test the greater the risk of false-negative results.

In the present study, carried out at the Westminster Medical School, London, the degrees of increase of S.G.O.T., S.L.D., and S.H.B.D. and the time during which increased levels persisted were determined in 20 patients with a confirmed diagnosis of myocardial infarction. The mean peak activities of S.G.O.T. and S.H.B.D. were approximately 4 to 5 times the upper limit of normal, while the mean peak value for S.L.D. was about 3 times the normal upper limit. The mean times for which abnormal findings were observed were 4 to 3 days for S.G.O.T., 8 to 0 days for S.L.D., and 13 to 3 days for S.H.B.D. The relative diagnostic efficacy of the 3 tests was compared by measuring the areas enclosed by the time-activity curves and the normal upper limits. They were in the ratio S.G.O.T. = 1.00 : S.L.D. = 1.06 : S.H.B.D. = 2.84. Accordingly, the S.H.B.D. is recommended as the most appropriate enzyme test at present available for the confirmation of suspected myocardial infarction.

Leon Gillis

1264. Inhibition of Vaccinal Hemagglutinins by Sera of Patients with Coronary Heart Disease and Other Chronic Illnesses

B. J. NEFF, W. W. ACKERMANN, F. H. EPSTEIN, and T. FRANCIS JR. *Circulation Research* [Circulat. Res.] 10, 836-845, June, 1962. 6 figs., 18 refs.

Vaccinal haemagglutinin (VHA) is a lipoprotein complex and is readily estimated by haemagglutination. It is inhibited *in vitro* by substances in the serum of patients who have been vaccinated and others subject to various pathological conditions. In this paper from the University of Michigan School of Public Health, Ann Arbor, it is suggested that alterations in the level of non-specific inhibition of VHA by substances in the serum might reflect metabolic disturbances in lipid metabolism related to atherosclerosis. [The basis of this assumption is questionable.]

To examine this theory the serum inhibitory titres to the agglutination of chicken erythrocytes by VHA were deter-

mined in persons with a variety of chronic diseases and in a control sample of the general population. [For experimental details reference should be made to the original paper.] It was found that between the ages of 30 and 74 raised titres occurred in 63% of men and 56% of women with chronic diseases, but in only 40% of men and 36% of women in the control series. Patients with coronary arterial disease tended to show the highest titre. The authors suggest that the serum inhibitor studied may reflect in part relatively "non-specific" pathological changes provoked by various biological stresses.

R. Wyburn-Mason

1265. A Comparison between Ultralow-frequency Ballistocardiograms and those Secured by an Improved High-frequency Technique, with Studies to Explain Remaining Differences

I. STARR and A. NOORDERGRAAF. *American Heart Journal* [Amer. Heart J.] 64, 79-100, July, 1962. 19 figs., 16 refs.

Most models of the ballistocardiograph are based on a recording of the displacement of the subject with each heart-beat whilst lying on a table that is either firmly fixed or held in place by a firm spring. The natural frequency of such a system is of the order of 12 cycles per second. The authors have been associated mainly with ballistocardiography employing a system of much lower natural frequency (0.12 cycle per second). In this, the subject lies on a light table suspended by long wires and the recording is of acceleration and not merely of displacement with each heart-beat.

The two types of recording are roughly similar, but this study attempts to explain the differences and to modify the high-frequency apparatus to make it more similar to the low-frequency model in its results. The biggest source of variation in the results obtained with the high-frequency model is due to movement taking place between the human body and the table; the more firmly the subject is fixed, the more similar do the recordings become. On the whole, the waves recorded with the high-frequency apparatus are taller and narrower and show less notching. Differences between the two types of recording are slight compared with their similarities.

J. A. Cosh

CONGENITAL HEART DISEASE

1266. Patent Ductus Arteriosus with Reversal of Flow in Adults

F. H. DAILEY, P. D. GENOVESE, and R. H. BEHNKE. *Annals of Internal Medicine* [Ann. Intern. Med.] 56, 865-882, June, 1962. 4 figs., 30 refs.

The authors, commenting that patent ductus arteriosus with reversal of flow is relatively uncommon, present a study of 41 cases reported in the literature and 6 new cases seen at Indiana Medical Center Hospitals, Indianapolis. Most patients had life-long dyspnoea, and haemoptysis, angina, and syncope were frequent. Hoarseness due to pressure on the left recurrent laryngeal nerve by a dilated pulmonary artery also occurred. Differential clubbing and cyanosis in which the right hand was usually spared was an important finding. There was evidence of polycythaemia and pulmonary hypertension with absence of the Gibson murmur. Radiological examination of the chest often revealed a large calcified pulmonary artery, and electrocardiography showed right ventricular hypertrophy or right

bundle-branch block. Cardiac catheterization demonstrated pulmonary hypertension, increased pulmonary resistance, and pulmonary flow less than systemic flow. The most useful diagnostic finding was a femoral arterial oxygen saturation less than simultaneous right brachial arterial saturation. The authors believe that in most patients pulmonary abnormalities are present from birth, and that these patients should never be subjected to surgery. *I. Ansell*

1267. Absence of the Pulmonary Valve with Ventricular Septal Defect

A. W. VENABLES. *British Heart Journal [Brit. Heart J.]* 24, 293-296, May, 1962. 2 figs., 7 refs.

The author describes 2 cases, seen at the Royal Children's Hospital, Melbourne, in which there was congenital absence of the pulmonary valve together with a ventricular septal defect. The presenting feature in both cases was intractable cardiac failure in infancy. Both had a loud, diffuse systolic murmur over the whole chest and a "to-and-fro" diastolic murmur maximal in the pulmonary area. Pulmonary valve closure was not audible. Peripheral arterial pulsation was of normal volume. Gross dilatation of the pulmonary trunk was found at necropsy in both cases. The author emphasizes that the features of these 2 cases closely resemble those in cases previously reported and constitute a clear-cut syndrome which can be diagnosed; also that diagnosis during life is important. Banding of the main pulmonary artery might be beneficial.

J. Warwick Buckler

1268. Hypoplasia of the Aorta and of the Branches of the Pulmonary Trunk: 2 Cases. (Hypoplasie de l'aorte et des branches de l'artère pulmonaire (Deux observations))

P. SOULIE, P. VERNANT, P. CORONE, F. BOUCHARD, J. FORMAN, E. ALBOU, and M. LEGENDRE. *Archives des maladies du cœur et des vaisseaux [Arch. Mal. Cœur]* 55, 436-450, April [received July], 1962. 13 figs., 4 refs.

The authors describe 2 cases of the rare association of hypoplasia of the aorta and of the branches of the pulmonary trunk. The first patient, a 5-year-old boy, was underweight, stunted, and mentally retarded. A cardiac lesion had been diagnosed at 3 months, but he had not suffered from dyspnoea on exertion and had never been jaundiced. The thorax was normal. There was a soft systolic murmur, of moderate intensity, best heard in the second intercostal space and radiating into the axillae. The second heart sound was accentuated. The electrocardiogram (ECG) showed right ventricular preponderance. Radiologically, the heart was enlarged to the right. Angiocardiography showed that the venous return in the right pulmonary artery was abnormal, and that the pulmonary trunk was normal in size but its branches were narrow. The ascending aorta was slightly and the descending aorta markedly hypoplastic. Cardiac catheterization showed a high systolic pressure (120 mm. Hg) in the right ventricle and in the pulmonary trunk above the "stenosis", and a sudden fall of pressure in both the pulmonary branches. Intracardiac phonocardiography recorded a loud systolic murmur below this fall in pressure.

The second patient, a 14½-year-old girl, was slightly underweight. A cardiac murmur and cardiomegaly had been noted when she was one year old. She had had no symptoms referable to the heart, until, at the age of 12, she had

suffered from infective endocarditis. The thorax was normal. She had a loud, rumbling systolic murmur, best heard in the second intercostal space and radiating along the vessels of the neck and into the left axilla and the back. At the height of the murmur the second heart sound was abolished. The ECG showed left ventricular preponderance. Radiologically, the whole heart was grossly enlarged, more to the left than to the right. Angiocardiography revealed a normal pulmonary trunk with marked thinning of the branches. There was an ampullary dilatation at the origin of the aorta, but the ascending part narrowed to only 8 mm. The aortic arch widened somewhat, but its branches were stenosed at their origin, and the descending aorta was abnormally narrow throughout. Catheterization showed stenosis of the middle portion of the branches of the pulmonary trunk. Systolic hypertension was noted in the right ventricle and in the pulmonary trunk and proximal portions of the branches. In the latter the diastolic pressure was low in comparison with the high systolic pressure. Intracardiac phonocardiography revealed a slight systolic souffle in the pulmonary trunk immediately after the occurrence of a sudden fall in pressure in the distal portions of its branches.

The authors were unable to eliminate the possibility that the second patient may have had a true aortic or subaortic stenosis, which would have helped to explain the fundamental semiological differences between the 2 cases. They are not satisfied with the theory that this malformation is linked embryologically with a normal partition occurring in a common but too small arterial trunk. In their cases the infundibulum and the pulmonary trunk, which arise from the common arterial trunk, did not appear to be abnormal. Hypoplasia was present only in the distal portions of the pulmonary arterial tree, which is derived from the primitive pulmonary plexus. Hypoplasia of the pulmonary trunk associated with hypoplasia of the aorta should be suspected in the presence of systolic bruits in both axillae and of radiological evidence of a narrowed aorta. The diagnosis of the condition is of no interest to heart surgeons, but is of interest to paediatricians dealing with poorly developed children whose condition is not considered, on clinical grounds alone, to be due to a cardiac abnormality. *E. S. Wyder*

CORONARY DISEASE AND MYOCARDIAL INFARCTION

1269. Anticoagulants in Heart Disease. (Antikoagulantien bei Herzkrankheiten)

F. KOLLER. *Schweizerische medizinische Wochenschrift [Schweiz. med. Wschr.]* 92, 769-776, June 23, 1962. 5 figs., 22 refs.

The author, writing from the University of Zürich, first points out that the chief, and undisputed, indication for the use of anticoagulants is venous thrombosis. Cor pulmonale following pulmonary embolism can be halted by long-term administration of anticoagulants, which are also effective in the prevention of embolism resulting from auricular fibrillation in rheumatic heart disease. The use of anticoagulants is reasonable in myocardial infarction, which in most cases results from coronary occlusion by a thrombus and in which a thrombus may form on the infarcted area and give rise to emboli in the limbs and lungs. They cannot be expected to have as spectacular an effect in arterial throm-

bosis, which is due to a vascular lesion, as in venous thrombosis, which is due to slowing and increased coagulability of the blood. Because it is impossible on the first day of an infarction to decide whether a patient is a good or a poor risk, the author recommends that all cases be given anticoagulants. In the acute phase, the mortality is 30 to 50% lower and embolic complications are 5 times less frequent in treated than in untreated cases.

After pointing out that comparison of treated and untreated cases requires a specially high order of statistical validity, with the danger of embolism receding 4 weeks after infarction and with anticoagulants having less effect in arterial than in venous thrombosis, the author then describes 189 cases he has treated [with no matching series of untreated controls]. He concludes that anticoagulants appear somewhat to lengthen life, but that they cannot be depended upon absolutely to prevent a recurrence of infarction. Yet he believes that where a first infarct appears imminent following repeated attacks of angina pectoris gravis, it can be prevented by the prophylactic long-term use of anticoagulants. The occurrence of myocardial infarction in haemophiliacs is not, he says, a valid argument against anticoagulant therapy. In the half-dozen cases in which this is known to have happened the haemophilia was mild, and Factor VIII was not entirely absent, as it is in classic cases. Moreover, anticoagulants affect the 4 factors, II, VII, IX, and X, of which IX is of most importance in the formation of thrombi. Provided cases are carefully selected and supervised and all necessary laboratory facilities are available, anticoagulant therapy is, in the author's view, relatively safe. In his 370 ambulant cases, liver damage had never occurred, allergic reactions had been uncommon, and a haemorrhagic diathesis had become manifest in only 31. E. S. Wyder

1270. Serious Hemorrhagic Complications of Anticoagulant Therapy

B. H. PASTOR, M. E. RESNICK, and T. RODMAN. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 747-751, June 2, 1962. 15 refs.

This paper describes 8 cases in which serious haemorrhage developed during anticoagulant therapy at the Veterans Administration Hospital, Philadelphia. These were as follows. (1) A fatal case with haematuria, ecchymosis of penis and scrotum, bloody pleural effusion and ascites, intrapulmonary haemorrhage, retroperitoneal haemorrhage, and bleeding into the bowel. (2) A non-fatal case with gastro-intestinal bleeding and extensive haematomata in subcutaneous sites; there was radiological demonstration of duodenal ulceration. (3) A fatal case of extensive intrapulmonary haemorrhage, with bleeding into the kidneys, ureters, bladder, and retroperitoneal tissues. (4) A non-fatal case with bleeding gums and haematuria. (5) A non-fatal case of gastro-intestinal bleeding, probably from a duodenal ulcer. (6) A non-fatal case of gastro-intestinal bleeding. (7) A non-fatal case of haemoptysis, haematuria, and melaena. (8) A fatal case of gastro-intestinal bleeding. The bleeding could be variously attributed to failure to ensure that the patient attended for review of therapy, lack of patient-cooperation, ingestion of salicylate, laboratory errors, failure to recognize clinical evidence of minor haemorrhagic phenomena, failure to appreciate preceding evidence of peptic ulceration, and concomitant use of corticosteroids.

[This is a valuable paper, both for the clinical accounts of haemorrhage and for the review of the literature, which should be read by those interested in anticoagulant therapy.]

A. S. Douglas

1271. ABO Blood Groups in Relation to Ischaemic Heart Disease

B. BRONTE-STEWART, M. C. BOTHA, and L. H. KRUT. *British Medical Journal* [Brit. med. J.] 1, 1646-1650, June 16, 1962. 18 refs.

The increasing incidence of ischaemic heart disease in certain countries has led to the view that its development is hastened by environmental factors. The object of this study, carried out at the University of Capetown, was to obtain data on the interplay of genetic and environmental factors in the development of this condition.

Blood groups were determined in 792 patients attending the prothrombin clinics of the Cape Peninsula, where the white population live side-by-side with a coloured population. The aim was to assess the ABO blood group pattern in ischaemic heart disease. This seemed simple at first but later turned out to be complex. Among the difficulties were (1) that the white population could not be regarded as homogeneous, and (2) that differences appeared according to whether the ischaemic heart disease first manifested itself as myocardial infarction or as angina pectoris. There was an excess of Groups A and B and a deficiency of Group O among the patients when compared with the controls. The extent of these deviations depended on the presence or absence of previous myocardial infarction and on the racial origin of the patient. In races in which the prevalence of ischaemic heart disease was high there was no significant deviation, and it was thought that this exemplified the complex interplay of genetic and environmental factors in the development of this disease.

Leon Gillis

1272. Lipid and Mineral Matter in Coronary Arteries and Aorta. I. Results in a Group of Men Dying from Causes Unrelated to Coronary Artery Disease

T. P. WHITEHEAD, M. K. ALEXANDER, D. F. BARROWCLIFF, A. P. PRIOR, and N. MARSH. *Journal of Atherosclerosis Research* [J. Atheroscler. Res.] 2, 199-209, May-June, 1962. 12 figs., 8 refs.

Working in the laboratories of the South Warwickshire Hospital Group, Warwick, the authors estimated the severity of atherosclerosis at different ages in a group of men who died from causes unrelated to occlusive coronary disease by analysing the lipid and mineral content of their coronary arteries and aortas. The arteries were obtained from routine necropsies. Patients who died from ischaemic heart disease or with severe hypertension, diabetes mellitus, or gross malnutrition were excluded.

The contents of total lipids and mineral matter were estimated for 81 aortas and 63 sets of coronary arteries. In 43 of the aortas and 40 of the coronary arteries a differential analysis of lipids was also performed. Total lipid was measured by extraction with absolute methanol and re-extraction with petroleum ether. The extracted artery was dried to constant weight, and incinerated with nitric acid to give the weight of the mineral matter. The extracted lipid was fractionated by chromatography on a silicic acid column. This yielded three main fractions: Fraction I contained the cholesterol esters; Fraction II contained free cholesterol and

triglycerides; and Fraction III contained mainly phospholipids.

In the aorta the total lipid content rises from a mean of 5.5 g. (per 100 g. dried organic material) below the age of 20 years to a mean of 12.2 g. at 65 years. In the coronary arteries the comparable figures are 12.5 g. rising to 19.9 g., a marked reduction in the rate of increase occurring, however, from 55 years onwards. The high total lipid content of the coronary arteries in early life is not due to any particular component. This is in contrast to the composition of aortic lipid in early life, when the phospholipid shows a marked preponderance over both cholesterol fractions. In later life the relative proportions of the fractions approach similar values for both arteries.

Both cholesterol and cholesterol ester in the aorta increase slowly during the early decades, but rise steeply after the age of 48 years. Together they represent approximately 20% of the total lipid at 18 years, rising to 60% by the age of 65, when they are present in approximately equal concentrations. The mean triglyceride fraction is unaltered throughout the period studied. The rise in concentration of cholesterol and cholesterol esters in the coronary arteries continues slowly and the mean triglyceride content of the coronary arteries declines with age, but the scatter of results is very wide.

In early life there is very little mineral matter in the aorta. With advancing age the mineral content increases steadily up to 55 years, when the process is accelerated. In the coronary arteries deposition is slower between 18 and 45 years, but after this age it is accelerated to over three times the rate in the aorta.

These observations show a considerable difference between the lipid content of the aorta and that of the coronary arteries early in life, presumably due to the difference in structure of their walls. The increase of lipid in both arteries with age is mainly due to deposition of cholesterol and cholesterol esters.

H. Caplan

1273. Lipid and Mineral Matter in Coronary Arteries and Aorta. II. Results in a Group of Men Dying from Coronary Artery Disease

T. P. WHITEHEAD, M. K. ALEXANDER, D. F. BARROWCLIFF, A. P. PRIOR, and N. MARSH. *Journal of Atherosclerosis Research* [J. Atheroscler. Res.] 2, 210-216, May-June, 1962. 6 figs., 1 ref.

Using the techniques described in their previous paper (see Abstract 1272) the authors analysed the total lipid and mineral content of 16 aortas, in 14 of which component lipids were determined, and the total lipid and mineral content and the lipid fractions in 26 sets of coronary arteries, of men who died of ischaemic heart disease.

The values for both lipid and mineral contents of the aortas in the group with coronary occlusion showed no significant differences from those of a control group of men who died from causes unrelated to this condition. There was a statistically significant increase in the mean total lipid content of the coronary arteries in the coronary occlusion group, the increase being principally in the cholesterol ester and free cholesterol components, and to a lesser extent in phospholipid. The mineral content of the coronary arteries in both controls and patients with coronary occlusion showed a striking increase in later life, the increase in the latter group beginning somewhat earlier.

In none of the factors determined was there any statistical difference between the results obtained from men who died with fresh occluding thrombus and those in whom none was demonstrable.

If it is accepted that the degree of atherosclerosis can be assessed by analysis of the lipid and mineral content of the arteries, this work gives quantitative confirmation to the view that patients dying of coronary arterial disease have a higher degree of coronary atherosclerosis than those dying from other causes. The findings also suggest that surveys of aortic lipid concentration and aortic atherosclerosis are of limited value in the epidemiology of ischaemic heart disease.

H. Caplan

1274. First Aid in Myocardial Infarction: An Experiment in Moscow. (Опыт оказания скорой помощи больным инфарктом миокарда в Москве)

S. G. MOISEEV. *Советская Медицина* [Sovetsk. Med.] 36, 30-35, June, 1962. 17 refs.

An efficient system of communication between practitioners, ambulance stations, and emergency departments of hospitals would help to reduce the mortality from coronary thrombosis. According to instructions issued to doctors in 1957 and 1960 by the Soviet Ministry of Health, the patient should be taken to hospital as soon as possible after the onset, wherever this occurs. A coronary thrombosis is followed immediately by a phase of shock or excitement of very short duration, which in turn is followed by a second or "torpid" phase of vascular collapse with fall of arterial and venous pressure. In Moscow ambulances specially equipped to combat this shock are available. They may be called by the regional doctor or, if the attack occurs in the street, by the police. They are provided with apparatus for electrocardiography, blood count, and determination of blood coagulation time and erythrocyte sedimentation rate, surgical instruments for transthoracic cardiac massage, apparatus for administration of oxygen and for artificial respiration, and a laryngoscope with intubators. Each ambulance has one or two doctors, in addition to the ambulance men, who give treatment by injections and any other appropriate measures until they are satisfied that the patient can safely be transferred to hospital. Private rooms specially equipped for such cases are available in 6 of the largest hospitals in Moscow. The hospital is warned of the patient's arrival by a radio message from the ambulance.

Of 315 patients with severe coronary thrombosis treated in these special ambulances, only 3 died before they reached hospital.

H. W. Swann

1275. Steroid Therapy in Heart-block following Myocardial Infarction

J. L. C. DALL and J. BUCHANAN. *Lancet* [Lancet] 2, 8-12, July 7, 1962. 2 figs., 23 refs.

Complete heart-block is a comparatively rare complication of myocardial infarction, probably because the conducting tissue has an independent blood supply from the right coronary artery and is therefore protected from damage in the course of septal infarction. When it does occur, however, the arrhythmia is dangerous and may prove rapidly fatal.

The authors here report the results of corticosteroid treatment in 12 cases of heart-block following myocardial infarction at the Victoria Infirmary, Glasgow. Seven

patients received prednisolone or dexamethasone by mouth, while 5 patients were given intravenous injections of hydrocortisone. Of the 7 patients treated orally, normal sinus rhythm was restored in 6 within 36 hours to 8 days after treatment was started. In this group 2 deaths occurred after sinus rhythm had been restored. Sinus rhythm returned to normal much more rapidly with intravenous therapy; the patients' condition was much improved, and only one death occurred without sinus rhythm being restored. The 5 cases so treated are described in detail.

The authors emphasize the importance of restoring normal sinus rhythm in these cases. They consider that intravenous hydrocortisone therapy gives better results in this regard than oral treatment with other corticosteroid preparations, and suggest that this form of therapy is worthy of further trial.

Leon Gillis

SYSTEMIC CIRCULATORY DISORDERS

1276. **Experimental Investigations and Therapeutic Use of Angiotensin.** (Experimentelle Untersuchungen und therapeutische Erfahrungen mit Angiotensin) P. LICHTLEN, F. SCHAUB, and A. BÜHLMANN. *Schweizerische medizinische Wochenschrift* [Schweiz. med. Wschr.] 92, 639-647, May 26, 1962. 3 figs., bibliography.

The demonstration of the identity of effect of the recently synthesized pressor substance angiotensin II and of its naturally occurring form has permitted a broader study of the former in human subjects. Its activity depends upon the end-position of phenylalanine in the molecule, the spatial relation of this amino acid with valine; the presence of a free carboxyl group, and the presence of the phenol group of tyrosine in Position 4. Angiotensinase, normally present in kidney, liver, and blood; alters the activity of angiotensin by altering the amino-acid sequence. In its chemical effects angiotensin, like vasopressin, produces a slight antidiuretic effect by increasing tubular resorption of water and causing an increased secretion of aldosterone. PAH clearance is unaffected. In high doses it can produce slight excitation of cardiac rhythm, but is in no way comparable with noradrenaline in this effect. Again in contrast to noradrenaline the concentration of angiotensin in the plasma is increased in hypertension, and this may be the reason for the increased plasma levels of aldosterone in malignant hypertension. The plasma level of angiotensin in shock is not yet known.

In investigations carried out at the University Medical Clinic, Zürich, 14 normal subjects received single and continuous (20-minute) infusions of angiotensin by means of cardiac catheterization. A slight rise in pulmonary arterial pressure and vascular resistance was demonstrated, while in the systemic circulation there was a rise in systolic and, to a lesser extent, diastolic blood pressure in linear relation with increasing dosage from 2.5 to 12.5 μg . per minute. The maximum effect was achieved in 30 seconds, with a systolic rise of 103 to 181 mm. Hg and a diastolic rise of 57 to 100 mm. Hg. There was no change in cardiac output, but there was a parallel fall in pulse rate.

A total of 51 patients (22 of them males; average age 51 years) were given infusions of angiotensin for the treatment of peripheral shock, each having a fall in systolic blood pressure of at least 90 mm. Hg lasting at least 30 minutes. No case of shock due to blood loss was included. The primary

disease was most commonly myocardial infarction, but the series included cases of hepatic coma, uraemia, sepsis, pulmonary embolism, and diabetic coma. In 41 cases at least an initial reversal of the shock was obtained with dosages ranging from 7 to more than 100 μg . per minute. There was a direct linear relation between the degree of shock and the dosage required to raise the pressure. The patients were grouped according to results as follows: (I) 39% of the total responded to pressor therapy and survived their primary disease; (II) 35% responded to therapy, but succumbed to their primary disease; (III) 6% made an initial response, but died from secondary shock; and (IV) 20% failed to respond at all. The average dosage necessary to obtain any effect in the last three groups, was 6 to 10 times higher than in Group I, in which the infusions were maintained, on average, for about 2½ days. No antidiuretic effect was noted, and the patients remained in positive fluid balance. Of 16 patients who received successive therapy with angiotensin and noradrenaline during the same period of shock, all required approximately equal dosages of the pressor drugs (48 μg . per minute for noradrenaline and 54 μg . per minute for angiotensin) to achieve an equipressor state, in contrast to the findings in normal subjects, who required less angiotensin than noradrenaline to produce an equivalent effect.

The authors conclude that the prime indication for the use of angiotensin is isovolaemic shock with peripheral vascular collapse. It is of no value in hypovolaemic shock, in which replacement therapy is essential, in cardiac shock with reduction in cardiac output and peripheral vasoconstriction, or in secondary (late) shock, which is still irreversible.

Allene Scott

BLOOD VESSELS

1277. **Long Term Anticoagulant Treatment in Atherosclerosis Obliterans of the Lower Extremities**

O. SELVAAG. *Journal of the Oslo City Hospitals* [J. Oslo Cy Hosp.] 12, 89-107, June, 1962. 1 fig., 8 refs.

The value of long-term anticoagulant therapy in atherosclerosis obliterans of the legs was studied at Ullevål Hospital, Oslo, in 82 patients, most of whom received dicoumarol (phenindione in "exceptional cases"), 84 similar patients who were not given anticoagulant therapy serving as controls. In the treated group the prothrombin-proconvertin (P-P) level was maintained in the 10 to 30% range for 80% of the time. None of the patients at the time of the first examination was over 70 years of age. The two groups were comparable as regards age of the patients, sex ratio, number of previous myocardial infarctions, and the incidence of severe ischaemia of the legs and feet shown by rest pain, ulceration, or gangrene. Both groups were followed up for periods varying from 5 to 9 years.

The incidence of hypertension (13 cases) was lower in the treated group than in the controls (24 cases) and the incidence of diabetes was similarly lower (3 cases compared with 7). However, the treated group showed a higher incidence of coronary arterial disease (27 cases compared with 16), a higher average serum cholesterol level (315 mg. per 100 ml. as against 280 mg. per 100 ml.), and a greater average duration of peripheral arterial insufficiency (34 months compared with 27 months). There were 36 deaths in the treated group, 32 of which were due to cardiovascular

causes, and 38 in the control group, 29 of which were due to cardiovascular disease. Mortality was higher in patients with pre-existing coronary arterial disease, severe peripheral arterial disease, diabetes, or hypertension than in those without these associated conditions.

The author states that long-term anticoagulant therapy did not "prevent the development of coronary artery disease in the different age groups or in groups with different serum cholesterol levels". Of 123 patients without coronary symptoms initially, coronary disease subsequently developed in 44 (angina, myocardial infarction, or sudden death). The incidence of cerebrovascular strokes was similar in the treated and control groups (8 and 11 cases respectively) and the course of the peripheral arterial insufficiency was also similar in the two groups.

The author concludes from his findings that there is no clear evidence of any benefit from long-term anticoagulant therapy as regards the progress of peripheral arterial disease or the development of complications in the coronary or cerebral circulation. However, anticoagulants may, in fact, have been of some value; in the first 5 years there was a lower mortality from cardiovascular conditions and more frequent improvement in intermittent claudication in the treated group than in the controls.

[This report should stimulate some re-thinking by those who favour long-term anticoagulant therapy for patients with occlusive vascular disease affecting the legs.]

T. B. Begg

1278. **Atherosclerosis and Nutrition.** [In English]
F. S. P. VAN BUCHEM. *Nutritio et dieta [Nutr. et Dieta (Basel)]* 4, 122-147, 1962. 5 figs., bibliography.

1279. **Atheroma of the Aorta and the Possible Role of Unsaturated Fatty Acid Deficiency in its Formation**
M. SANDLER and G. H. BOURNE. *Nature [Nature (Lond.)]* 193, 1184-1185, March 24, 1962. 3 figs., 12 refs.

The normal lipids of the arterial wall do not differ from the lipids of atheromatous lesions, at least initially. Moreover, arterial tissues can synthesize all the constituents of the advanced lesions. Thus some metabolic derangement of the arterial wall might well produce the atheroma.

The authors of this paper from Emory University, Atlanta, Georgia, state that histochemical studies of 5-nucleotidase and adenosine triphosphatase (ATP) in the young human aortic wall have shown a strong uniform reaction over the whole length of the aorta for both enzymes. In older atheromatous aortas the activity of both enzymes was greatly reduced even in areas where no histological evidence of an atheromatous change was present. Essential-fatty-acid-free diets produce aortic atheroma in rats. ATP activity was found to be decreased in certain aortic spots in fatty-acid-deficient rats after 4 weeks on the diet, and these spots gradually increased in size until the whole length of the aorta became negative for ATP. No change in other phosphatases was observed. Only after 12 weeks on a deficient diet did the characteristic sudan black lipoidal deposits appear in the intima. The enzyme change thus precedes the deposition of lipids and the ATP-free spots may actually correspond to pre-atheromatous areas.

It has been shown that a significant portion of the cholesterol present in the aorta is synthesized locally; and in the biosynthesis of cholesterol ATP is necessary for the phosphorylation and also for the decarboxylation of mevalonic

acid phosphates. Thus the tissues may control the biosynthesis of cholesterol by regulating the availability of ATP. The decrease of ATP in the pre-atheromatous spots and in atheroma may thus pave the metabolic pathway for increased cholesterol biosynthesis.

The arterial wall seems to synthesize a significant part of the lipids which accumulate in atheroma. Evidence from animal experiments and human necropsy studies suggests that the initiating factor may be a deficiency of essential fatty acid. It is suggested that a raised blood cholesterol level is probably only a contributing and not an initiating factor in atheroma formation.

Z. A. Leitner

1280. **Buerger's Disease: a Distinct Clinical and Pathologic Entity**

V. A. MCKUSICK, W. S. HARRIS, O. E. OTTESEN, R. M. GOODMAN, W. M. SHELLEY, and R. D. BLOODWELL. *Journal of the American Medical Association [J. Amer. med. Ass.]* 181, 5-12, July 7, 1962. 12 figs., 22 refs.

The authors of this paper from Johns Hopkins Hospital and University, Baltimore, present evidence to refute the view, which has gained increasing support in recent years, that Buerger's disease is merely precocious atherosclerosis.

Buerger's disease has been observed frequently in Korea and Japan. In 20 out of 28 cases seen in Korea onset was before the age of 35. One or both arms were involved in 17. All the patients were heavy cigarette smokers, and exacerbations could be produced by even one or two cigarettes. The electrocardiogram, serum cholesterol level, and fasting blood sugar level were normal; eggs and dairy products were not eaten. Most of the men worked in rice paddies, with their hands and feet in cold water and subject to trauma and even frostbite; Raynaud's phenomenon was not observed. Changes typical of atherosclerosis were not seen in 24 arteriograms from 15 subjects, but other changes were present in both arms and legs. The results of 9 histopathological studies of amputated limbs were similar. In Korea and Japan coronary arterial disease, atherosclerotic aortic disease, phlebothrombosis, and post operative pulmonary embolism are rare.

The ages of, and the clinical picture in, 12 patients studied in Baltimore resembled those in the patients seen in Korea and Japan. Arteriograms showed no stenosis or obstruction in the large vessels to the limbs and no intimal irregularities as in atherosclerosis. However, 11 out of 14 brachial arteriograms and 14 out of 17 femoral arteriograms did reveal such abnormalities as occlusion or recanalized vessels. The appearances differed from those of embolism, 3 cases of which were also studied by arteriography. In Baltimore, 33 specimens (31 from amputations and 2 taken for biopsy) from 10 patients were studied histologically. There was no significant atherosclerosis. The arteries and veins were commonly the site of organized, recanalized thrombi, and in 6 patients an "acute characteristic lesion" of Buerger's disease—that is, small, multiple micro-abscesses in a fresh or organizing thrombus—was present. The micro-abscesses contained polymorphonuclear leucocytes, mononuclear epithelioid cells, and multinuclear giant cells; no micro-organisms were seen. There was chronic inflammatory infiltrate in the vessel wall, but no necrosis as in arteritis. The authors suggest that the histological appearances are more compatible with an abnormality of blood than an anomaly of the vessel wall.

T. B. Begg

Clinical Haematology

1281. The Plasma Clearance of Daily Doses of Folic Acid in Megaloblastic Anaemia

I. CHANARIN and M. C. BENNETT. *British Journal of Haematology* [Brit. J. Haemat.] 8, 95-109, April, 1962. 10 figs., 26 refs.

At St. Mary's Hospital, London, the rate of plasma clearance and the urinary excretion of folic acid were observed after daily intravenous injections of 15 μ g. of folic acid per kg. body weight in 18 patients with megaloblastic haemopoiesis (pernicious anaemia 7; pregnancy 2; steatorrhoea 5; post-gastrectomy 1; and associated with chronic lymphatic leukaemia in one, with melanomatosis in one, and with carcinoma of the stomach in one). These values were also studied in 5 healthy controls and 9 patients with disorders such as myelofibrosis, malignant disease, and chronic skin disease.

It was found that more folic acid was retained for the first few days by patients with megaloblastic erythropoiesis, the retention being due to folic-acid deficiency. It was also found that more folic acid was retained after the 5th day, particularly in patients with megaloblastic anaemia, and also in one patient with chronic eczema. This was not due to previous vitamin-B₁₂ therapy and it did not appear to be due to folic-acid deficiency. The authors suggest that it may be due to an increased capacity to incorporate folic acid into the coenzyme form.

R. B. Thompson

1282. The Thalassemias: Variants and Roentgen Bone Changes

J. E. MOSELEY. *Journal of the Mount Sinai Hospital* [J. Mt Sinai Hosp.] 29, 199-214, May-June, 1962. 11 figs., 18 refs.

The author of this paper from Mount Sinai Hospital, New York, discusses the bone changes seen radiologically in association with the thalassaemias. He points out that the recent developments in our knowledge of the abnormal haemoglobins and their inheritance have tended to distract attention from the associated bone changes. Many different forms of thalassaemia are now recognized, but how far they are all associated with skeletal abnormalities has not yet been determined. As a rule skeletal changes in thalassaemia are not very marked during the first year of life although they have been observed as early as 4½ months of age. The earliest changes are found in the metacarpals and metatarsals. In thalassaemia major these changes are generally in excess of those which are usually seen in the other chronic haemolytic anaemias, such as sickle-cell and spherocytic anaemia or the reticuloses. Changes in the skull, which may occur in some cases of iron-deficiency anaemia, are not associated with changes in the long bones. The author emphasizes that retardation of pneumatization of the air cells and swelling of the upper maxilla, when seen, may be considered of first importance in differentiating thalassaemia from sickle-cell or spherocytic anaemia. In patients who survive infancy there is regression of the changes in the skeleton as age advances. Thalassaemias, other than thalassaemia major, can clearly produce skeletal changes; the author describes one or two instances, but the frequency

of their occurrence is not yet clear. Routine skeletal radiographs in all cases of an abnormal haemoglobin syndrome should give important information.

Janet Vaughan

1283. Exchange Transfusion in the Treatment of Erythroblastosis Foetalis Caused by Rhesus Antagonism. (De betekenis van de wisseltransfusie bij de therapie van erythroblastosis foetalis door rhesus-antagonisme)

H. P. C. M. HOYNCK VAN PAPENDRECHT and P. G. HART. *Nederlands tijdschrift voor geneeskunde* [Ned. T. Geneesk.] 106, 1134-1138, June 2, 1962. 27 refs.

The treatment by exchange transfusion of erythroblastosis foetalis caused by rhesus antagonism was investigated at the University of Utrecht. Between January 1, 1949, and January 1, 1960, 142 women who were rhesus-negative and who had been immunized against D antigen gave birth to 145 children, including 3 sets of twins. Only 14 of these infants were rhesus-negative; 28 were stillborn. Of the remaining 103 born alive, 45 received one or more exchange transfusions. The infants were transfused through the umbilical vein, by means of a thin Nélaton catheter (size 6 or 7), with 500 ml. of rhesus-negative blood of the appropriate group to which 0.4 ml. of heparin and 20 ml. of physiological saline had been added. To neutralize the heparin 5 mg. of protamine sulphate was given by the same route. All the infants had morbus haemolyticus neonatorum before transfusion. Of the 45 children 23 received one transfusion each, 14 received 2, 4 received 3, 2 received 5, and 2 received, respectively, 6 and 9 transfusions. All the infants survived. In 39 of the cases kept under observation, no deleterious effects followed exchange transfusion or morbus haemolyticus neonatorum.

Anne Tothill

NEOPLASTIC DISEASES

1284. Critical Evaluation of Massive Steroid Therapy of Acute Leukemia

E. SHANBROM and S. MILLER. *New England Journal of Medicine* [New Engl. J. Med.] 266, 1354-1358, June 28, 1962. 3 figs., 14 refs.

At the City of Hope Medical Center, Duarte, California, 57 patients with acute leukaemia of various types have been given massive corticosteroid therapy. A modified "double-blind" method was employed in 43 cases, the usual treatment being either 50 mg. or 500 mg. prednisolone daily for 10 days. Many of the patients had previously had other forms of treatment and some had been treated with corticosteroids. In the differentiation of acute lymphocytic leukaemia from the granulocytic or monocytic variety, special importance was attached to the occurrence of Auer bodies. Acute leukaemia was considered to be of lymphocytic type in 25 cases, of granulocytic type in 22, monocytic in 9, and plasma-cell leukaemia in one case.

Many of the patients receiving the larger dose of prednisolone had initial subjective improvement, but only those with acute lymphocytic leukaemia had objective evidence of

benefit. In cases of acute lymphocytic leukaemia sensitive to corticosteroid, improvement occurred more rapidly with the larger dose, but there is no evidence that the smaller dose would not eventually have produced the same effects, except perhaps in a few cases when the disease had become resistant to the smaller dose. Massive therapy was associated with deterioration in 11 patients with acute granulocytic or monocytic leukaemia. Septicaemia, rectal abscess, and gastrointestinal haemorrhage were frequent complications in patients receiving the larger dose.

The authors conclude that there is no evidence that corticosteroid therapy produces haematological improvement in acute granulocytic or monocytic leukaemia, whatever the doses employed. On the contrary, they believe that in all kinds of acute leukaemia massive corticosteroid therapy may prove harmful by increasing the frequency of complications, especially of severe infections. Attention is drawn to the fact that previous reports of the advantages of massive corticosteroid therapy in acute leukaemia have not mentioned different effects on different morphological types of the disease.

A. G. Baikie

1285. Seasonal Variation in the Clinical Onset of Leukaemia in Young People

J. A. H. LEE. *British Medical Journal* [Brit. med. J.] 1, 1737-1738, June 23, 1962. 2 figs., 6 refs.

The author reports from the Social Medicine Research Unit (Medical Research Council) at the London Hospital a study of the seasonal variations in the incidence of leukaemia in young people. The month of occurrence of the first symptom of leukaemia (mostly acute) was ascertained for 1,671 patients aged 0 to 19 years from record cards completed by the participating hospitals and sent to the National Cancer Registration Scheme of England and Wales. It was found that in both sexes a significantly greater number of cases had their onset in the summer months, with a peak in June (χ^2 30.24, D.F. 11, $P < 0.005$). The seasonal variation was not so marked if the month of diagnosis was used for the computation; it was evident in all age groups, but not significant by the χ^2 test in the group 0 to 4 years. In 1,081 cases the cell type was specified, and it would appear that only the lymphoblastic type of leukaemia shows a seasonal onset.

R. B. Thompson

1286. Study of Complete Remission in Acute Leukaemia. (Étude de la rémission complète des leucémies aiguës)

J. BERNARD, M. BOIRON, M. WEIL, J. P. LEVY, M. SELIGMANN, and Y. NAJEAN. *Nouvelle revue française d'hématologie* [Nouv. Rev. franç. Hémat.] 2, 195-222, March-April [received June], 1962. 6 figs., bibliography.

The occurrence of complete remission in acute leukaemia must be regarded as one of the most remarkable events in clinical haematology. This paper from the Saint Louis Hospital, Paris, describes complete remission in 126 of 300 cases of acute leukaemia treated in the period 1956-60. The criteria of complete remission were strict, and included the clinical condition and the results of examination of the peripheral blood and of the bone marrow. The acute leukaemia was regarded as lymphoblastic in type in 60% of the cases, and patients with this form accounted for 88% of those who had a complete remission. Of 72 patients under the age of 5 years complete remission was obtained in 48. The incidence of complete remission declined with age and

none was obtained in patients over the age of 60. This is not attributable solely to the lower frequency of lymphoblastic leukaemia in older people.

In lymphoblastic leukaemia the treatment most often resulting in complete remission was prednisone in a dosage of 3 mg. per kg. body weight per day, while in myeloblastic leukaemia the most effective treatment was prednisone combined with amethopterin. The administration of corticosteroid and 6-mercaptopurine simultaneously did not, in the small number of cases so treated, give better results in lymphoblastic leukaemia than a large dose of corticosteroid alone. On the other hand, there is evidence that the longest remissions were obtained when treatment with prednisone was followed by maintenance therapy with 6-mercaptopurine. In 35% of cases of lymphoblastic leukaemia in which complete remission was obtained a second remission was induced after relapse. It seems that both the frequency and perhaps the duration of remissions may be greater in young children than in older patients. The authors discuss the general significance of complete remission in acute leukaemia and the possible mechanisms of relapse.

[This paper should be read in the original by all interested in the natural history of leukaemia.]

A. G. Baikie

1287. Treatment of Hodgkin's Disease and Other Malignant Reticuloses by Vincalencoblastine. (Essai de traitement de la maladie de Hodgkin et d'autres affections réticulo-histiocytaires malignes par la vincalencoblastine)

G. MATHE, O. SCHWEISGUTH, G. BRULE, J. L. AMIEL, A. CATTAN, M. THOMAS, and P. ZAMET. *Presse médicale* [Presse méd.] 70, 1349-1352, June 2, 1962. 8 figs., 18 refs.

A trial of vincalencoblastine (vinblastine) in the treatment of Hodgkin's disease and allied disorders is reported from the Institut Gustave-Roussy, Villejuif, France. The drug was given intravenously in an initial dosage of 0.1 to 0.15 mg. per kg. body weight per week, this being later increased to 0.2 mg. per kg. sometimes twice weekly. The patients treated were those with Hodgkin's disease (22), reticulum-cell sarcoma or lymphosarcoma (5), and mycosis fungoides (3) in whom x-ray treatment alone was considered unlikely to give long remission. The most important side-effect was leucopenia, which invariably occurred a few days after each injection but quickly subsided. There were no gastrointestinal or neurological side-effects. Of 24 courses of treatment for Hodgkin's disease given to 22 patients, 7 produced complete and 9 partial remission. In the other diseases partial remission occurred in 2 cases of sarcoma and one of mycosis fungoides. The authors suggest that remission can be obtained by injection of vinblastine in cases of Hodgkin's disease which are "resistant" to x-ray therapy and alkylating agents.

K. E. Halnan

1288. Clinical Experience with Vincalencoblastine in Far-advanced Hodgkin's Disease and Various Malignant States

J. W. FROST, M. I. GOLDWEIN, and J. A. BRYAN. *Annals of Internal Medicine* [Ann. intern. Med.] 56, 854-859, June, 1962. 7 refs.

The authors report their experience with vincalencoblastine (vinblastine) in the treatment of 22 patients with advanced Hodgkin's disease and 11 patients with other malignant diseases at the Hospital of the University of Pennsylvania, Philadelphia. Two methods of dosage were used—"massive" doses of 0.3 to 0.6 mg. per kg. body weight given

intravenously over 3 days, or "low" doses of 0.1 to 0.2 mg. per kg. every one or 2 weeks for 6 weeks or longer.

Only slight benefit was seen in any patients except those with Hodgkin's disease, but among the latter an objective response was observed in 6 of 12 patients given massive doses and in 2 of 10 patients given low doses. In a few patients who responded the disease later recurred, but was again controlled by a maintenance dosage of 0.1 mg. per kg. given every 2 weeks. Side-effects of the treatment included leucopenia, nausea, constipation, anxiety, and paraesthesiae in the feet. Marked leucopenia and sepsis occurred in 7 patients, of whom 4 died.

The authors emphasize that only patients with far-advanced disease refractory to other methods of treatment were included in the trial. They state that "the marked variability of response to the drug as expressed by the leukocyte count, and the dangers accompanying severe leucopenia, made individualization of dosage and careful control imperative".

K. E. Halnan

BLOOD TRANSFUSION

1289. The Production of Anti-human-globulin Sera of Different Specificities in Rabbits. [In English]
G. H. FAIRLEY and G. HARRIS. *Vox sanguinis [Vox Sang. (Basel)]* 7, 175-189, 1962. 4 figs., 24 refs.

The authors, from the Postgraduate Medical School of London, describe the sera currently in use in blood-group work: (1) "Antiglobulin serum", reacting with γ -globulin, complement, or other non- γ -globulins on the surface of erythrocytes; (2) "anti- γ serum", reacting only with γ -globulin-coated erythrocytes; and (3) "anti-non- γ serum", reacting with erythrocytes coated with complement or other non- γ -globulins, but not with γ -globulin. An attempt was made to prepare these sera by the method of Milgrom *et al.* (*Nature*, 1956, 177, 329). Rabbit erythrocytes were incubated respectively with γ -globulin Fraction G3, with pooled, undiluted, heat-inactivated human serum, and with dilute, pooled, heat-inactivated human serum and re-injected into the donor rabbits during one to 3 immunization courses. The maximum duration was 48 days. The methods used are briefly outlined. The sera so obtained were tested by immunoelectrophoresis, and against erythrocytes sensitized by a variety of blood-group antibodies and cells from patients with autoimmune haemolytic anaemia. Survival of the re-injected erythrocytes was also studied, with radioactive chromium and by a fluorescent protein-labelling method. Sera against γ -globulin-coated erythrocytes reacted with Rh-sensitized cells and those of 2 patients with autoimmune haemolytic anaemia of the warm antibody type, but not with those of a cold antibody type. They reacted also with some complement-binding antibody. Immunoelectrophoresis showed γ , α_2 , and β_2 M lines. Sera against re-injected erythrocytes coated with undiluted, heat-inactivated pooled human serum were of antiglobulin type, had a titre of 32,000 to 64,000 after 2 courses of injections (37 days) and acted against γ -coated and complement-coated test cells and also against cells sensitized with incomplete anti-D, -Le^a, -K, and -Fy^a. The heterophil antihuman titre of these sera did not exceed 8 and could be eliminated by dilution. Immunoelectrophoresis gave the same lines as the preceding serum but also β_1 lines. Coating the cells

for re-injection with dilute, pooled, heat-inactivated human serum did not have a disadvantage of the preceding method, in which these cells agglutinated spontaneously in saline. The serum so produced was also an antiglobulin serum with the same range of activity as that in the preceding group. More injections were found necessary than in the preceding group. The dilution of the incubating serum necessary to prevent subsequent autoagglutination of the sensitized cells was found to be 1:16.

The advantage of this method lies in the ability to produce antiglobulin serum in a relatively short time with the use of human serum only. No animal failed to respond to this technique and none showed any ill effects. F. Hillman

1290. The Collection and Preservation of Blood. Methods of Collection and Preservation and Suggested Procedures for Improving Its Quality for Massive Transfusions
H. SWAN and D. C. SCHECHTER. *Archives of Surgery [Arch. Surg.]* 84, 599-607, June, 1962. 1 fig., bibliography.

This paper from the University of Colorado School of Medicine, Denver, describes the sequelae of blood transfusion attributable to the extracellular electrolyte moiety. Methods of preserving blood for transfusion are reviewed and the collection of cord blood and of cadaver blood and the deep freezing of glycerolized erythrocytes are mentioned. Procedures in which citrate is used are discussed in more detail, and drawbacks, particularly in massive transfusions or on priming apparatus for extracorporeal circulation, are considered in the light of published work. Hypocalcaemia, hyperkalaemia and hyperammonaemia, citrate intoxication, and the effect of oxypurines and measures to prevent these are referred to. The authors also mention the addition of inosine to rejuvenate erythrocytes, the use of an alcohol-glucose-citrate solution, widely employed in Russia, and citrate-free processes in which heparin, resin decalcification, and chelation are used.

In the final part of the paper the method suggested by the authors is outlined and shown in a diagram. Bank blood [presumably in acid-citrate-dextrose solution] is heparinized and is then percolated through a monobed resin arrangement consisting of "(a) Dowex 50-X8, calcium cycle; (b) Dowex 50-X2, bicarbonate cycle, and (c) a resin sequestering nitrogenous products by the physicochemical phenomenon of 'ion-exclusion'". The first of these reduces sodium, potassium, magnesium, and ammonia, the second citrate, chloride, phosphate, and sulphate, and the last free haemoglobin and oxypurines. The effluent blood contains heparin, bicarbonate, and calcium. Oxygenation at this stage will further increase the pH. The authors consider that this system may become incorporated into a disposable unit and act as filter, resin column, and drip chamber.

F. Hillman

1291. Blood Groups and Disease: Previous Transfusion as a Potential Source of Error in Blood Typing

C. A. CLARKE, W. T. A. DONOHUE, R. B. MCCONNELL, J. H. MARTINDALE, and P. M. SHEPPARD. *British Medical Journal [Brit. med. J.]* 1, 1734-1736, June 23, 1962. 2 refs.

Recently a number of surveys have been made of the incidence of various blood groups in different conditions. The fact that the blood group of the patient may have been affected by previous transfusion seems to be important, especially in those conditions, such as duodenal ulcer, in

which multiple transfusions are commonly given. It is well known that following a transfusion of ABO and D compatible blood, other antigens of the rhesus system or other group—for example, MN—different from that of the patient's original blood group can be detected. The present authors, working at the University and the Royal Infirmary, Liverpool, have studied this problem both *in vitro* and *in vivo*. They found that after adding one part of blood to nine parts of blood of a different genotype, the minor sample of blood could always be detected in the mixtures. Of 12 patients examined who had had blood transfusions an apparent change in the genotype was detected in 11; the remaining patient had blood which happened to be identical in the rhesus and MN groups. These changes could easily be detected for 4 weeks after the transfusion. It is usually possible to detect this apparent change because of the appearance of mixed-cell population, but for the unwary or inexperienced this may be missed and the reaction scored as positive.

The authors calculate the frequencies of possible changes in genotypes of the rhesus and MN system following transfusions and show that, in fact, the calculated frequencies following transfusion would match the reported instances in certain blood-group surveys. Although their argument is not necessarily conclusive for all surveys, it is obvious that previous transfusion of patients who are included in these surveys could drastically affect the results.

R. F. Jennison

HAEMAGGLUTINATION

1292. Haemophilia Minor; 17 Cases. (L'hémophilie mineure (à propos de 17 observations))
M. GOUEMAND, M. FOUCAUT, A. HUTIN, and A. PARQUET-GERNEZ. *Lille médical* [Lille méd.] 7, 448-456, May [received July], 1962. 16 refs.

The authors, writing from the Pasteur Institute, Lille, France, report 17 cases of haemophilia minor, 10 of Type A and 7 of Type B. All the patients had a minor haemorrhage following accidental trauma, operation, or dental extraction. Prothrombin consumption was altered in 14 of the 17 cases and the response to Bigg's test was altered in all. Antihæmophilic globulin level was always lowered, the mean being 19.3% for Factor A and 8.25% for B; this distinguished the cases from those of major haemophilia. Treatment was with blood or fresh plasma in both types.

Arnold Pines

1293. Willebrand's Disease; 7 Cases. (La maladie de Willebrand (à propos de sept observations))
M. GOUEMAND, M. FOUCAUT, A. PARQUET-GERNEZ, and A. HUTIN. *Lille médical* [Lille méd.] 7, 457-463, May [received July], 1962. 15 refs.

This paper describes 7 cases of Willebrand's disease. The haemorrhages began in infancy in all the cases, very often with apparently spontaneous mucous or skin bleeding, and were either minor or major in degree. Investigation of the families of 2 of the patients showed that other members were affected. The only constant finding was lowering of anti-hæmophilic globulin level, which ranged in the 7 patients from 7 to 62%. Cortisone and plasma transfusions proved useful in reducing haemorrhage.

Arnold Pines

1294. Female Transmitters of Haemophilia A. (Les conductrices de l'hémophilie A)

M. GOUEMAND, M. FOUCAUT, A. HUTIN, A. PARQUET-GERNEZ, and G. MACKEY-VERMELLE. *Lille médical* [Lille méd.] 7, 469-475, May [received July], 1962. 2 figs., 21 refs.

The authors, at the Pasteur Institute, Lille, France, determined the antihæmophilic globulin (A.H.G.) levels in 29 mothers of subjects with classic haemophilia A. They divided the mothers into: (1) "certain transmitters", 17 in number, in whose families at least 2 members (2 children, or one child and one other member) were known hæmophiliacs; and (2) "possible transmitters", 12 in number, of whom one child was a known hæmophiliac but in whose families no other case was known. The mean A.H.G. level was 49% in the "certain transmitters", 65% in the "possible transmitters", and 84% in 23 normal women. In 5 of the "certain transmitters" the A.H.G. level was normal. It is concluded, therefore, that an A.H.G. level below 50% in repeated estimations in a woman belonging to a hæmophilic family indicates that she is capable of transmitting the disease, and that a woman with a normal A.H.G. level may transmit the condition to her children.

Arnold Pines

1295. Blood Coagulation and Barbiturates. (Hemocoagulación y barbitúricos)

J. F. MORENO and A. A. R. GARCÍA. *Clinica y laboratorio* [Clin. y Lab.] 73, 401-416, June, 1962. 3 figs., 22 refs.

This is a study of the effect of 0.3 g. of phenobarbitone on blood coagulation in over 300 surgical cases at the Military Hospital, Saragossa, Spain. The following were estimated: clotting time, bleeding time, accelerated clotting and prothrombin times, fibrinolysis, antistreptolysin titre, clot retraction, thromboplastin generation, and the platelet count. In a series of patients these values were estimated before the induction of general anaesthesia and again at the conclusion of the operation. The drugs most often used were pethidine (500 mg.), promethazine (0.25 g.), chlorpromazine (0.25 g.), and thiopentone sodium (0.75 g.). Barbiturates were found to cause only negligible increase in coagulability, which remained within physiological limits. In patients requiring treatment with anticoagulants, the barbiturate did not interfere with the action of these drugs. In the authors' view there is no objection to the administration of anaesthetics, sedatives, or hypnotics at the same time as anticoagulants.

A. Schott

1296. The Acceleration of Thrombus Formation by Certain Fatty Acids

W. E. CONNOR. *Journal of Clinical Investigation* [J. clin. Invest.] 41, 1199-1205, June, 1962. 3 figs., 23 refs.

The author, at the State University of Iowa College of Medicine, Iowa City, set out to study the effects of fatty acids on the coagulation of blood. A method was used in which artificial thrombi similar in microscopical appearance to those occurring in human thromboembolic disease were made in a rotating circular plastic tube. The sodium salts of many different fatty acids were added to human blood in the apparatus and the time of thrombus formation was measured. It was found that long-chain saturated fatty acids greatly accelerated thrombus formation, while short-chain saturated fatty acids and long-chain unsaturated fatty acids affected it little or not at all.

A. Brown

Respiratory System

1297. **Fatal Alveolar Proteinosis with Pulmonary Fibrosis.** (Protéinoase alvéolaire mortelle associée à une fibrose pulmonaire)

J. BRUN, M. PERRIN-FAYOLLE, M. TOMMASI, R. QUENTIN, and H. POZZETTO. *Revue lyonnaise de médecine [Rev. Lyon. Méd.]* 11, 491-500, April 15 [received July], 1962. 4 figs., 19 refs.

An account is given, from the University of Lyons, of the first French case of pulmonary alveolar proteinosis to be reported complete with necropsy findings. This rare disease of unknown aetiology was first described by Rosen (*New Engl. J. Med.*, 1958, 258, 1123), and the present authors have found fewer than 100 cases reported in the world literature. The patient was a man of 72 with severe progressive dyspnoea. Radiological examination showed widespread pulmonary shadowing. He died 3 years after the first clinical manifestations of the disease, and the diagnosis was made from the histological findings in the lungs. These consisted essentially of pulmonary fibrosis and filling of the alveoli by an eosinophil substance which gave a strongly positive periodic-acid-Schiff reaction but did not stain with mucicarmine.

Bernard Isaacs

1298. **Erythropoiesis and Ferrokinetics in Chronic Respiratory Disease**

M. LERTZMAN, L. G. ISRAELS, and R. M. CHERNIACK. *Annals of Internal Medicine [Ann. Intern. Med.]* 56, 821-833, June, 1962. 4 figs., 32 refs.

Since chronic exposure to high altitude in normal subjects leads to secondary polycythaemia which is roughly proportional to the degree of hypoxia, whereas patients who are hypoxic from disease do not always appear to develop a comparable degree of polycythaemia, the authors, working at the University of Manitoba and the General and Children's Hospitals, Winnipeg, studied the erythropoietic response of 11 normal subjects and 25 patients who had chronic hypoxia (12 with bronchitis and emphysema, 2 with "primary" emphysema, one with honeycomb lung, one with tuberculosis, 7 with obesity, and 2 with congenital heart disease). They report lung function studies in their subjects as well as haematological and blood volume studies, using dye dilution or radioactive-iodinated serum albumin for plasma volume, and erythrocytes labelled with radioactive chromium (^{51}Cr) for erythrocyte mass measurements. The plasma iron turnover rate was calculated from the rate of disappearance of injected radioactive iron and serum iron concentration, and calculations were made of the rate of incorporation of iron for erythrocyte formation.

They found that the patients with hypoxia did in fact develop secondary polycythaemia which was roughly proportional to the hypoxic stimulus, but that this could be masked by changes in plasma volume. Thus secondary polycythaemia can be present with a normal haematocrit and is best demonstrated by measuring the total erythrocyte mass. There was a direct relationship between the reduction of arterial oxygen tension and a quick disappearance rate of radioactive iron from the plasma, but patients with bronchitis and emphysema had a delayed and incomplete

incorporation of radioactive iron into the erythrocytes. The cause of the latter finding was not apparent.

P. Hugh-Jones

1299. **Steroid Therapy in Chronic Bronchitis**

M. CLIFTON and C. H. STUART-HARRIS. *Lancet [Lancet]* 1, 1311-1313, June 23, 1962. 1 fig., 17 refs.

At the Royal Hospital, Sheffield, 28 patients with chronic bronchitis were treated with steroids, mostly prednisolone, starting with 30 mg. daily, with reduction to a maintenance dose of 5 to 15 mg. daily. Ten patients showed no subjective improvement and in 3 the response was doubtful, but 15 showed varying degrees of improvement, in particular a reduction in breathlessness and wheezing. In only 3 patients was the response dramatic; in 19 of the 28 the treatment was discontinued.

Ventilatory capacity was determined by measuring the forced expiratory volume in the first $\frac{1}{4}$ second of expiration (F.E.V._{0.75}) in 23 patients. In 3 this index declined with steroid therapy, in 5 it showed no change, and in the remaining 15 there was an increase of between 20% and 136%, but only 9 of these showed subjective improvement. The mean increase in all the patients was 36%. After several months' treatment the mean F.E.V. in all patients was significantly higher than at the outset. In a few patients the total lung volume and residual volume were measured, but the changes in these indices did not parallel the changes in ventilatory capacity. Over-all, the F.E.V. increased by 20% or more within a week in two-thirds of the patients, the increase being by 60% or more in 7 patients. In only 6 patients was continuation of treatment accompanied by continued increase in F.E.V. The authors conclude that although their results indicate that steroids can improve the ventilatory capacity of some patients with chronic bronchitis, the ultimate benefit to most patients is doubtful.

C. M. Fletcher

1300. **Spirographic Profile in Chronic Bronchitis.** (Profil spirographique de la bronchite chronique)

P. SADOUL, I. KIRIN, C. SAUNIER, and F. SCHRIJEN. *Folia medica [Folia med. (Plovdiv)]* 4, 5-12, 1962. 4 figs., 25 refs.

The authors, at the University of Nancy, made a spirographic study of 221 cases of chronic bronchitis in men aged 40 to 60. The series did not include patients with pneumoconiosis or pulmonary congestion secondary to heart disease, but did include those with attacks of nocturnal dyspnoea. All the patients had suffered for at least 5 years from winter episodes, lasting 2 or more weeks; of cough with mucopurulent sputum. In addition, 98 normal controls were investigated in the same way. Measurements included vital capacity (V.C.), forced expiratory volume per second (F.E.V.), and residual volume (R.V.). Pharmacodynamic tests were carried out in which patients inhaled in the form of an aerosol the bronchoconstrictor drug acetylcholine, 1 in 10,000, for 3 minutes, and the bronchodilator drug isoprenaline sulphate ("aléudrin"), 1 in 200, for 5 minutes, the F.E.V. being measured before and after inhalation. However, the methods used did not permit assessment of the duration or the purulence of the expectoration. Bronchitic

subjects without dyspnoea or purulent expectoration showed increased sensitivity to acetylcholine only, but their spirographic spectrum was similar to that of normal controls. In patients with moderate dyspnoea and mucopurulent or purulent sputum there was slight diminution of the F.E.V. and of the V.C., while the R.V. was at the upper limit of normal. Patients with severe bronchitis and frequent purulent expectoration showed the spirographic spectrum of emphysema with a slight decrease in V.C., an absolute and relative decrease in F.E.V., and positive responses to acetylcholine and aleudrin tests.

K. Zinnemann

1301. Comparative Evaluation of Clinical and Necropsy Findings in Bronchiectasis. (Vergleichende Auswertungen klinisch und autopsisch bestätigter Bronchiektasen)

R. SCHUBERT, F. ENDERLE, and E. BIHLMAIER. *Deutsches Archiv für klinische Medizin* [Dtsch. Arch. klin. Med.] 208, 206-226, 1962. 8 figs., 48 refs.

Analysing the records of the 2,123 necropsies performed at the University Medical Clinic, Tübingen, Germany, during the years 1947-59, the authors found 200 cases (140 male, 60 female) with a post-mortem diagnosis of bronchiectasis, in only 30 of which the diagnosis had been made during life. The majority of the deaths had occurred in the age group 65 to 75. This peak is 10 years later than that reported in previous papers, a change which is probably due to the use of antibiotics. Chronic cor pulmonale was present in 105 cases and had been the cause of death in 55. These 55 had a 25- to 35-year history of lung disease and a quarter of them had some evidence of asthma, whereas the remaining 145 had only a 5- to 15-year history and no marked incidence of asthma. Cases of chronic cor pulmonale had, in addition to bronchiectasis, complications causing pulmonary hypertension, such as emphysema, bronchitis, lung fibrosis, and kyphoscoliosis. Pulmonary tuberculosis was present in 22 of the 200 cases. The incidence of bronchial carcinoma was 10%, which was double that in cases without bronchiectasis. There was an even higher incidence of cancer in cases of bronchiectasis with asthma, but the series was too small for these figures to be statistically significant.

D. Goldman

1302. A Comparison of Spirometric and Peak Expiratory Flow Measurements in Men With and Without Chronic Bronchitis

A. S. FAIRBAIRN, C. M. FLETCHER, C. M. TINKER, and C. H. WOOD. *Thorax* [Thorax] 17, 168-174, June, 1962. 1 fig., 15 refs.

During a survey of London Post Office workers the authors have compared the merits of several simple tests of air-flow obstruction in discriminating between subjects with and those without bronchitis. Tests were confined to samples of men, as few women had symptoms of the disease. In the 143 postmen (aged 40 to 59 years) selected for study spirometry was carried out and peak expiratory flow (P.E.F.) was estimated by a Wright expiratory flowmeter (Wright and McKerrow, *Brit. med. J.*, 1959, 2, 1041; *Abstr. Wld Med.*, 1960, 27, 459). At spirometry the following indices were recorded: forced expiratory volume in one second (F.E.V._{1.0}); maximum mid-expiratory flow (M.M.F.); forced vital capacity (F.V.C.); vital capacity (V.C.); and the forced expiratory volume as a percentage of either the V.C. or the F.V.C., whichever was the greater (F.E.V.%).

Of the 143 men studied, 91 could not be classified definitely in either the normal or the bronchitic group. Among the remaining 52 subjects were 35 regarded as normal (with no history of cough, expectoration, or chest illness in the last 3 years) and 17 with bronchitis ("sputum with recurrent infection"). In these 52 men it was found, on the basis of a "t" test [for details of this test the original paper should be consulted], that the F.E.V. and M.M.F. were the most discriminating tests in consistently separating normal from bronchitic subjects. The F.E.V.% (often used by American workers) was less discriminating. The authors conclude that the F.E.V., which is simpler to measure than the M.M.F., is the most discriminating test of ventilatory obstruction for use in epidemiological studies of chronic bronchitis. The inter-correlation between all these tests is given, and it is shown that the F.E.V. can be predicted from the P.E.F. readings by multiplying the latter (in millilitres) by 4 and adding 600. Since, however, the correlation between P.E.F. and F.E.V. is only $r = +0.8$ for men (and lower for women) there is a wide scatter about the average F.E.V. predicted in this way.

P. Hugh-Jones

1303. Physical Education in Early Childhood for the Prevention of Pneumonia. (Влияние физического воспитания на снижение заболеваемости детей раннего возраста)

M. I. FANAREV. *Педиатрия* [Pediatrya] 41, 11-15, July, 1962. 11 refs.

In a study conducted among 800 children in the paediatric clinics of Volkhov the author observed that physical education, combined with attention to hygiene and a rational diet, reduced to one-third the incidence and gravity of pneumonia in children under the age of one year. The physical education, which took the form mainly of gymnastic exercises, was initiated by health visitors and then entrusted to the parents.

A. Orley

1304. The Prognosis of Severe Respiratory Insufficiency in Emphysematous Patients. (Zur Prognose lebensbedrohlicher respiratorischer Insuffizienzen Emphysemkranker)

G. WEIMANN. *Deutsches Archiv für klinische Medizin* [Dtsch. Arch. klin. Med.] 208, 171-178, 1962. 22 refs.

The author, writing from the University of Giessen, Germany, reports a study of prognostic factors in 18 patients who were dangerously ill with respiratory insufficiency due to emphysema and cor pulmonale. The arterial blood oxygen and carbon dioxide content and oxygen capacity were determined by the Van Slyke method. Gas tension and alkali reserve were deduced from nomograms. These blood gas analyses indicated the severity of the illness, the degree of hypoxaemia, and hypercapnia if present, but did not help with the prognosis in individual cases. Factors associated with an unfavourable prognosis were an arterial oxygen content of less than 12 volumes %, arteriosclerosis in the older patients, bronchitis, pneumonitis, right heart failure, and a poor response to cardiac glycosides in patients with cor pulmonale. Early treatment of pulmonary infection may improve lung ventilation and so ameliorate hypoxaemia and alveolar hypoventilation. Oxygen helps to reduce hypoxaemia, while changes in acid-base balance also need correction. Cor pulmonale may be relieved by strophanthin or by digitalis and diuretics.

D. Goldman

Urogenital System

1305. Acute Urinary Infections: Their Course and Outcome in General Practice with Special Reference to Chronic Pyelonephritis

J. FRY, J. B. DILLANE, C. L. JOINER, and J. D. WILLIAMS. *Lancet* [Lancet] 1, 1318-1321, June 23, 1962. 1 fig., 6 refs.

During the years 1955 to 1957 the rate of occurrence of acute urinary infection in a general practice was about 12 per 1,000. The incidence was 4 times greater in females than in males. There was a peak in young women (20 to 30 age group), with constant high levels thereafter. Males were more commonly affected after the age of 40. Of 172 original patients, 40 had removed from the practice by 1961; of the remaining 132, 125 replied to a letter and questionnaire and brought a further specimen of urine for examination. Of these 125 patients (27 males and 98 females), 32 (4 males and 28 females) had required treatment for further attacks of acute urinary infection. On preliminary testing the urine of 54 of the 125 patients showed some abnormality, and these were further examined. Six of the 54 were children but only one (a girl aged 4 who had had 3 attacks of acute urinary infection) had persistent abnormality. Of the 48 adults, 19 had persistent abnormality. One was a patient with orthostatic proteinuria and the others had pus cells and bacteria in the urine. Intravenous pyelography was carried out in 14 cases and renal biopsy in one. There were 9 women with recurrent cystitis without serious underlying cause, 3 women with possible chronic pyelonephritis, and 5 men with either prostatic enlargement or urethral stricture. The authors state that their data "do not suggest that recurrent and persistent urinary infection has led to chronic pyelonephritis in these patients".

K. G. Lowe

1306. The Effect of Haemodialysis on the Chemistry of the Serum and Cerebrospinal Fluid in Uraemia. (Die Beeinflussung des Liquorchemismus durch Hämodialyse beim urämischen Patienten)

W. SCHETTLIN and A. HUNZIKER. *Schweizerische medizinische Wochenschrift* [Schweiz. med. Wschr.] 92, 673-676, June 2, 1962. 10 refs.

The authors, writing from the University of Zürich, point out that haemodialysis will speedily restore the electrolyte balance in patients with acute uraemia, with consequent improvement in the clinical abnormalities. However, before improvement takes place, some 6 to 24 hours after the end of dialysis, neurological symptoms may appear, the level of consciousness may become depressed, and the patient may even become comatose. This discrepancy between the ready correction of serum electrolyte disturbance on the one hand and neurological deterioration on the other led the authors to investigate simultaneously the chemistry of the serum and of the cerebrospinal fluid (C.S.F.) in 7 patients with acute renal failure who were undergoing haemodialysis. The urea concentration in the serum fell to 30% of the original value, and in the C.S.F. to 80% of the original value. Osmolarities changed with urea concentrations. Before dialysis the serum osmolarities averaged 12 mOsm.

per litre higher than the C.S.F. osmolarities; after dialysis the gradient was reversed. This must be followed by water uptake into the C.S.F.-brain space, which would account for the temporary depression of the mental state at a time when other clinical features are improving.

G. W. Csonka

1307. On the Specificity of the Manifestation of Chronic Glomerulonephritis in Children. [In English]

T. TAKATSU and H. SATO. *Annales paediatrici* [Ann. paediat. (Basel)] 199, 366-392, 1962. 12 figs., bibliography.

The authors describe their findings in 82 children with "chronic glomerulonephritis" observed at Tokyo University Hospital during the period 1954-61. Over the same period there were 157 children with "acute glomerulonephritis" and 51 with "pure nephritis". On the basis of the clinical picture the cases of chronic disease were classified as follows: (1) "classic" chronic glomerulonephritis (38 cases); (2) "nephrotic nephritis" (32 cases); (3) "asymptomatic proteinuria" (9 cases); and (4) "cyclic vomiting" (3 cases). To illustrate these groups 11 typical cases are described in detail together with the biopsy findings.

[This paper is not easy to summarize, and there are certain difficulties. "Nephrotic nephritis" is classified separately from "pure nephrosis" on the basis of haematuria, hypertension, and renal insufficiency, but the follow-up of "pure nephrosis" is not reported. The patients described as having "chronic glomerulonephritis with asymptomatic proteinuria" had normal plasma protein and non-protein nitrogen levels, normal renal function, and showed only minor histological abnormality of the glomeruli. The proposed classification is certainly no better than others based on clinical and biopsy findings, without adequate follow-up over the years.]

D. A. K. Black

1308. Late Recurrences of the Nephrotic Syndrome: Recurrence after Prolonged Remissions Induced by Adrenal Steroid Therapy

H. G. WORTHEN, A. F. MICHAEL, R. L. VERNIER, and R. A. GOOD. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 103, 794-802, June, 1962. 7 figs., 19 refs.

This paper from the Variety Club Heart Hospital, University of Minnesota, recounts the clinical course of 5 children with the nephrotic syndrome in whom there was recurrence of proteinuria and oedema after remission of 12 to 45 months induced by adrenal steroid therapy. Renal biopsy, carried out on 3 of the 5 children, showed no changes on light microscopy, and the glomerular filtration rate in all 5 was normal or increased. In one patient relapses coincided with attacks of hay-fever. In none of the patients did the relapses imply a bad ultimate prognosis.

D. A. K. Black

1309. Nephrocalcinosis in Children: Review of the Literature and Report of a Case Complicated by Wilms's Tumour

E. M. BATESON. *Clinical Radiology* [Clin. Radiol.] 13, 231-237, July, 1962. 6 figs., bibliography.

Endocrinology

1310. The Ability of Plasma Proteins to Bind Calcium in Normal Subjects, in Patients with Primary Hyperparathyroidism Both Pre- and Post-operatively, and in Other Hypercalcaemic Conditions

H. M. LLOYD, G. A. ROSE, and D. SMEENK. *Clinical Science [Clin. Sci.]* 22, 353-362, June, 1962. 2 figs., 19 refs.

It was shown in a previous study (Lloyd and Rose, *Lancet*, 1958, 2, 1258; *Abstr. Wld Med.*, 1959, 26, 34) that active parathyroid chief-cell adenoma is always accompanied by a raised plasma level of ionized calcium, even though the total plasma calcium level might be normal, and that parathyroid hormone can diminish the power of the plasma proteins to bind calcium. The present paper, from University College Hospital, London, "endeavours to show that the reduction in ability of plasma proteins to bind calcium is seen only in hypercalcaemia due to primary hyperparathyroidism and that this may be expressed mathematically". The authors have given mathematical consideration to the ionized and protein-bound calcium in the plasma from 16 normal subjects and from 38 patients with hypercalcaemia due either to primary hyperparathyroidism (26) or to other causes (12). Plasma calcium fractions were determined by the method of Rose (*Clin. chim. Acta*, 1957, 2, 227) as modified by Fanconi and Rose (*Quart. J. Med.*, 1958, 27, 463). In their mathematical consideration the authors have accepted the view of McLean and Hastings (*J. biol. Chem.*, 1935, 108, 285) that in normal plasma the relationship between the ionized and protein-bound calcium could be expressed by the equation

$$\frac{[\text{Ca}^{++}] \times [\text{Prot.}]}{[\text{CaProt.}]} = K = 0.00892 \text{ at } 25^\circ \text{ C. and pH } 7.35$$

where [] = concentration in moles per kg. water; Prot. = dissociated base-combining group of proteins expressed as equivalents divided by 2. The authors express all values for plasma calcium fractions in terms of plasma water.

In 16 normal subjects the mean value of plasma ionized calcium was 6.13 mg. per 100 ml. and the mean of normal protein-bound calcium was 3.66 mg. per 100 ml. with a calculated mean value for $K_{\text{CaProt.}}$ of 0.0135. In 26 patients with primary hyperparathyroidism the mean value for the expression $100 \times \text{observed/calculated protein-bound calcium}$ was 90.4. In 17 of the cases after surgical relief of the hyperparathyroidism the mean value for $100 \times \text{observed/calculated protein-bound calcium}$ was 113.7. In 12 patients with hypercalcaemia not due to primary hyperparathyroidism the mean value for this expression was 111.0. The differences revealed in these groups were all shown to be statistically highly significant. The expression $100 \times \text{observed/calculated protein-bound calcium}$ is a measure of the ability of plasma proteins to bind calcium, the normal being taken as 100 with a standard deviation of 9.5. The results show that this ability of plasma proteins to bind calcium is reduced in patients with primary hyperparathy-

roidism and increased in the same patients after surgical relief of the condition.

The authors conclude that in hypercalcaemia due to causes other than primary hyperparathyroidism there is no diminution in the ability of plasma proteins to bind calcium. This is in contradiction of the view of other workers that the diminution of protein-binding of calcium is a function of hypercalcaemia, regardless of its cause. The authors consider that, with further refinement of technique, the measurement of plasma calcium fractions may provide a method of differentiating between hypercalcaemia due to primary hyperparathyroidism and hypercalcaemia due to other causes. Preliminary studies indicate that the same diminished ability of plasma protein to bind calcium occurs in secondary as in primary hyperparathyroidism. The authors therefore suggest that in various groups of subjects the parathyroid status may be assessed by measurement of plasma calcium fractions.

John Lister

1311. Treatment of Underweight Senile Patients with Anabolic Hormone

J. B. NIELSEN. *Danish Medical Bulletin [Dan. med. Bull.]* 9, 33-38, April [received June], 1962. 1 fig., 26 refs.

At the Mental Hospital, Vordingborg, Denmark, methandienone was given in a dosage of 6 mg. daily by mouth to 20 female patients (average age 80 years) all of whom were suffering from senile or arteriosclerotic dementia, a double-blind technique being used. The patients were emaciated (average initial weight 45 kg.) and had poor appetites. In addition they had various somatic disorders such as cardiovascular disease, urinary tract infections, intestinal disturbances, and anaemia. During the trial 5 patients died. The 15 survivors gained weight, this being more marked during treatment with the active substance than during administration of a placebo. The average gain during 20 weeks (8 of drug therapy) was 2.5 kg., 5% of the initial weight. In 6 patients activity increased and in 5 appetite improved. There was no definite change in the serum protein and the haemoglobin levels or in the erythrocyte sedimentation rate (E.S.R.). Free periods were arranged in order to ascertain whether the drug had fluid-retaining properties and whether weight gain would continue, but no definite conclusion was reached.

A second trial of the drug was carried out for 2 months on 33 similar but less debilitated patients (average age 75 years, average weight 47 kg.). Mental improvement was observed in 50%, there being some conformity between the mental improvement and the weight gain. Of the 33 patients 26 gained more than 2% of their original weight during the 2 months. No virilization was observed and there was no change in E.S.R., serum protein level, or the results of liver and renal function tests, but there was a slight increase in the haemoglobin value. Since all previous attempts to improve the weight of these patients had failed, the author concludes that the methandienone was responsible for the weight gain, partly by improving the utilization of protein and partly by improving appetite.

A. Gordon Beckett

PITUITARY GLAND

1312. Dexamethasone Suppression Test in Diagnosis of Cushing's Syndrome

J. D. H. SLATER, M. HARTOG, R. FRASER, and B. RANTZEN. *British Medical Journal* [Brit. med. J.] 1, 1584-1586, June 9, 1962. 1 fig., 14 refs.

This paper from the Postgraduate Medical School of London reports an investigation of the dexamethasone suppression test in the diagnosis of Cushing's syndrome. From the subjects studied the urine was collected for 2 consecutive 24-hour periods. They were then given dexamethasone in doses of 0.5 or 1 mg. every 6 hours for 7 days. Further 24-hour collections of urine were made on the 6th and 7th days of the period during which dexamethasone was given. 17-Ketogenic steroid excretion was estimated in all the 24-hour collections of urine.

In 9 normal subjects, 7 patients with idiopathic hirsutism, and 4 patients with menstrual disorders the 17-ketogenic steroid excretion had fallen to 2 mg. or less per 24 hours on the 6th and 7th days of dexamethasone treatment. In 24 obese subjects a similar fall in 17-ketogenic steroid excretion was noted, but 8 of these patients required the higher dose of dexamethasone before the level of ketogenic steroid excretion fell to 2 mg. or less per 24 hours. In 6 patients with Cushing's syndrome there was a much smaller decrease in 17-ketogenic steroid excretion. Only one patient showed a figure of less than 10 mg. per 24 hours on the 6th day and in this case the level was 11 mg. per 24 hours on the 7th day. After implantation of radioactive gold into the pituitary fossa 4 of the patients with Cushing's syndrome showed a good clinical remission. In these 4 the suppression test revealed levels of 17-ketogenic steroid excretion of 1 mg. or less per 24 hours. One patient showed only a partial clinical remission and suppression with dexamethasone produced 17-ketogenic steroid excretion of 7 and 6 mg. per 24 hours on the 6th and 7th days. One patient did not improve with radioactive gold implantation and the 17-ketogenic steroid excretion on the 5th and 6th days after dexamethasone therapy was 16 and 17 mg. respectively per 24 hours.

The authors conclude that the dexamethasone suppression test is of value in the diagnosis of Cushing's syndrome.

Charles Rolland

1313. Corticotropin Production Response to Methopyrapone: Response in Children to Adrenal Blocking Agent Methopyrapone (SU 4885)

I. H. GANS and R. A. ULSTROM. *American Journal of Diseases of Children* [Amer. J. Dis. Child.] 104, 258-268, Sept., 1962. 21 refs.

1314. The Surgical Treatment of Cushing's Syndrome following Bilateral Adrenal Hyperplasia. (Zur chirurgischen Behandlung des Cushing-Syndroms infolge bilateraler Nebennierenrindenhyperplasie)

L. ZUKSCHWERDT, M. G. GIEBEL, H. OETJEN, and J. TAMM. *Schweizerische medizinische Wochenschrift* [Schweiz. med. Wschr.] 92, 667-673, June 2, 1962. Bibliography.

This report from the University of Hamburg concerns 14 patients in whom a diagnosis of bilateral adrenal hyperplasia was made by study according to the method of Tamm *et al.* (*Acta endocr. (Kbh.)*, 1961, 37, 253) of the 17-hydroxycorticosteroids in the plasma and in the urine during a standardized infusion of 50 i.u. of adrenocorticotrophic hormone. There

were 7 males and 7 females and their ages ranged from 16 to 53, the majority being between 30 and 40. In 6 cases one adrenal gland (in 5 cases the left) was removed; in 8 cases both glands were removed in one operation, which was carried out with the patient in the ventral decubitus and by means of a dorsal approach and resection of the eleventh ribs. In the 6 patients (5 female) who underwent unilateral adrenalectomy there was no permanent improvement. A boy of 16 developed signs of an intrasellar tumour which, together with the signs of the Cushing syndrome, disappeared after pituitary irradiation (5,400 r.) 7 months after the operation. One woman (aged 32) died a month later from pulmonary embolism; another woman (aged 34) died, 11 months after the operation, following physical exertion, the symptoms of Cushing's disease having recurred; a third woman (aged 38) died from heart failure 5 days after the third (and 2 years after the first) operation. Of the 8 patients (2 females, 6 males) who had bilateral adrenalectomy followed immediately by substitution therapy, 2 males died; one of these, aged 36, died 4 days after the operation, and necropsy disclosed severe myocardial damage; the other, aged 31, died 20 months later with high blood pressure and probably from cerebral haemorrhage. In the remaining 6 patients there was considerable improvement in the symptoms due to Cushing's disease.

Considering both their own cases and those reported by others, the authors conclude (from a total of 17 cases) that the failure rate in unilateral adrenalectomy is 88%. Of 190 reported cases of bilateral subtotal adrenalectomy, 24 (13%) had recurrences, 5 (2.6%) had postoperative pituitary tumours, and substitution therapy had to be given in 80 (42%). Of 89 patients (including the 8 reported here) who underwent bilateral total adrenalectomy, 14 (16%) developed intrasellar tumours. Bilateral subtotal adrenalectomy carries the considerable risk of, in addition to recurrences, postoperative adrenocortical insufficiency, which is difficult to control.

[An interesting paper, but the conclusions drawn from the combined figures (the present cases plus those of other authors) are difficult to prove, since it is not clear how uniform the experience of the other authors was.]

V. C. Medvei

THYROID GLAND

1315. Puncture Biopsy of the Thyroid: Analysis of 60 Specimens. (Intérêt diagnostique de la ponction-biopsie de la thyroïde. Analyse de 60 prélèvements)

M. NAGEL. *Bruxelles-médical* [Brux.-méd.] 42, 853-864, July 1, 1962. 7 refs.

The author, writing from the University of Brussels, reports on 60 puncture biopsies of the thyroid gland. The technique used is described in detail. The author recommends that the procedure be carried out without premedication, that iodine should not be used to disinfect the skin, and that the patient should be lying down, the neck being placed in hyperextension by means of a cushion under the shoulders. The trocar (the May-Netter type with side-window and guillotine) is introduced obliquely so as to avoid damage to the trachea. When the thyroid parenchyma is penetrated blood should issue from the needle, unless the gland is sclerosed. Issue of fluid instead of blood indicates that the needle point is in a cyst. The most likely

complication, local haematoma, should be rare if due care is taken. Of the 60 cases examined, 17 were of simple hyperplastic goitre (14 euthyroid, 3 hyperthyroid), 28 of nodular goitre (20 uninodular, 8 multinodular), and 15 of diffuse indurated goitre. The last group included 9 goitres due to various forms of thyroiditis (2 with lymphocytic infiltration) and 3 due to thyroid carcinoma. Of the nodular goitres, one-third were adenomatous, one-third cystic, and the rest of varied origin (for example, Hodgkin's disease). The majority of the nodules were benign. Puncture biopsy, used in conjunction with the radioiodine test, autoimmune reactions, and other appropriate investigations, helps to differentiate between diffuse and nodular goitres.

V. C. Medvei

1316. **Studies on Effect of D-Thyroxine on Normal Subjects** R. BARNES, J. A. P. TRAFFORD, and P. M. F. BISHOP. *British Medical Journal* [Brit. med. J.] 2, 20-22, July 7, 1962. 14 refs.

At Guy's Hospital, London, 51 euthyroid individuals volunteered to take part in a double-blind trial to determine the effect of D-thyroxine on the blood cholesterol level and thyroid function of normal subjects. The effects of a 4-mg. tablet of D-thyroxine given twice daily for one month in 32 cases were compared with those of a placebo tablet of identical appearance given for the same period in the remaining 19 cases.

The serum cholesterol level fell in 30 of the 32 subjects who received D-thyroxine. The reduction was approximately proportional to the initial level, the average decrease being 48 mg. per 100 ml. A significant fall occurred in only one of the 19 subjects receiving the placebo. No significant change in basal metabolic rate was observed after treatment either in the controls or 23 treated subjects who were examined in this way. Such variations in weight as occurred were small and of no consistent pattern in either group. Depression of radioactive iodine uptake was not seen in the controls, but was noted in all except 2 of 17 treated subjects. The results thus provide evidence, contrary to previous studies, that D-thyroxine can reduce the serum cholesterol level of normal euthyroid subjects without inducing significant loss of weight or rise in basal metabolic rate.

H.-J. B. Galbraith

1317. **The Clinical Picture and Treatment of Hashimoto's Struma.** (К клинике и лечению струмы Хасимото) I. A. SAMILEV. *Проблемы Эндокринологии и Гормонотерапии* [Probl. Endokr. Gormonoter.] 8, 95-104, July-Aug., 1962. 21 refs.

The author discusses 6 personal cases of Hashimoto's struma and 19 other cases of this rare disease reported in the Soviet literature. Hashimoto's struma is a lymphoid thyroiditis, in contrast to Riedel's struma which is a fibrosis with atrophy of the parenchyma. Some authors (for example, Akimov and Levit) regard Hashimoto's struma as the early phase of a thyroiditis which later develops into the Riedel type; Breitman, Maslov, and Nikolaev, on the other hand, regard it as an entirely separate disease. Of the total of 25 patients, 23 were women, of whom only 3 were aged under 46 and only one over 60. Of the author's own patients, 5 had had a goitre for 5 years or more, but in several of the earlier cases reported in the literature goitre had been present for 3 months to 2 years. Thyroid func-

tion may be normal, depressed, or increased. The erythrocyte sedimentation rate is always raised. The thyroid swelling may be generalized, confined to one lobe, or nodular. In only one of the 19 reported cases was the correct diagnosis made before operation. In many cases malignancy was suspected; other diagnoses were Riedel's struma, nodular goitre, and parenchymatous goitre. In 2 of the author's patients the nature of the condition was revealed before operation by biopsy and histological examination, which he recommends in all suspected cases. He favours conservative resection by Nikolaev's method, and states that administration of thyroid extract is nearly always required after operation.

L. Firman-Edwards

1318. **Autoimmune Disease of the Thyroid and Colon, with a Report of a Case of Chronic Ulcerative Colitis in Association with Hashimoto's Disease and Penicillin Allergy** K. S. BREARLEY and A. S. D. SPIERS. *Medical Journal of Australia* [Med. J. Austr.] 1, 789-795, May 26, 1962. 2 figs., 44 refs.

The various theories concerning autoimmune disease are discussed. A case is then described (the first, according to the authors, to be reported in the literature) in which both Hashimoto's thyroiditis and chronic ulcerative colitis were present. The patient, a female aged 38 when admitted to the Royal Melbourne Hospital, Parkville, Victoria, in 1961, also had eosinophilia, allergy to penicillin, and a past history of unexplained venous thrombosis for which ligation of the inferior vena cava was required. She was neurotic, and the authors suggest that psychosomatic mechanisms may be important in autoimmune disease.

G. L. Asherson

1319. **The Use of Hexonium [Hexamethonium] in the Pre-operative Treatment of Patients with Thyrotoxicosis.** (Применение гексония в предоперационной подготовке больных тиреотоксикозом) JU, N. TURBIN. *Проблемы Эндокринологии и Гормонотерапии* [Probl. Endokr. Gormonoter.] 8, 73-76, May-June, 1962. 12 refs.

Of the ganglion-blocking preparations that have been widely used in surgical practice, hexamethonium has achieved considerable success. Villiner and Wilflingsender (1955) employed it in the preoperative preparation of patients with Graves's disease. Smirnov (1956) showed that it reduces the assimilation of radioactive iodine by the thyroid gland. The present author has used hexonium, a preparation of the drug made in the Kharkov Institute of Experimental Endocrinology, in 60 patients with various types of thyrotoxicosis—14 severe and 46 of moderate severity. The duration of the disease varied from 6 months (16 cases) to 3 years and upwards (27 cases). The drug was administered by subcutaneous injection, 1 ml. of a 2.5% solution being given 3 times daily for one to 3 weeks before, and for 2 to 3 days after, operation. The patient was kept in the recumbent position for 2 hours after each injection, to avoid hypotonia and collapse. The results were striking: weight rose by 1 to 5 kg. in 31 cases; the pulse rate fell by 10 to 60 beats per minute in 48 cases (the remaining 12 had little or no tachycardia before treatment); systolic blood pressure fell by 5 to 60 mm. Hg in 32 cases (the 28 others had normal arterial pressure); and the basal metabolic rate fell in 56 cases by an average of 13%. Side-effects occurred in 5

patients; these cleared up in 3 when the dose was halved, but in the remaining 2 the drug had to be withdrawn.

L. Firman-Edwards

ADRENAL GLANDS

1320. **The Histochemical Study of Adrenaline in the Adrenals and Paraganglia of Man in Relation to Their Development and Involution.** (Гистохимическое изучение адреналина в надпочечниках и парангангиях человека в связи с их развитием и редукцией)

N. M. KOVRIŽKO. *Проблемы Эндокринологий и Гормонотерапий* [Probl. Endokr. Gormonoter.] 8, 107-113, July-Aug., 1962. 4 figs., 32 refs.

Adrenaline formed in the chromaffin cells of the adrenal medulla can be identified by the chromic acid test, which was described by Henle in 1865, and also, according to the author, by Betz of Kiev University in 1864. Since then other methods of staining tissues for adrenaline have been developed by Schmori (modified by Sevki, 1934), Wiesel (1907), and Vulpian and Ogata (modified by Molchanova).

The author has studied the bodies of 30 children who died at ages up to 10 years. He examined the adrenal medulla and the superior abdominal aortic and the inferior supracardiac paraganglia, staining sections by all the above methods and also with silver impregnation by the methods of Bielschowsky-Gros and Gömöri, in addition to the usual haematoxylin-eosin, Mallory, and picrofuchsin stains. In newborn infants the tests were positive in all the paraganglia, but in the adrenals there was hardly any medullary substance. Small quantities of chromaffin cells were found in the medulla at 4 to 7 months in some cases. Up to the end of the first year there was a progressive increase in chromaffin tissue in the paraganglia, but in the latter half of the second year there was evidence of involution, although some chromaffin tissue was found in older children of 7 to 10 years. From the third to the tenth year the adrenal chromaffin tissue became increasingly evident. It therefore appears that all these organs are elements of a single system producing the same hormone. [The paper contains 4 photomicrographs showing the dominant role of the paraganglia as compared with the adrenal medulla in adrenaline formation in the first year of life.] L. Firman-Edwards

1321. **Prophylaxis with Corticosteroids in Surgical Patients Receiving Cortisone or Other Steroid Therapy.** [In English] J. H. SOLEM and I. LUND. *Acta anaesthesiologica Scandinavica* [Acta anaesth. scand.] 6, 99-105, 1962. 4 refs.

The keystone to a favourable outcome of a surgical operation in steroid-treated patients is to make sure that such patients without exception are registered as "a steroid case" before operation. It was found advantageous to let the responsibility of obtaining information about previous medication and of prophylactic corticosteroid treatment rest with the anaesthetist in charge of the case.

During the last 4 years the following scheme was adopted in Ullevål Hospital. Patients who had received corticoids within the last 4 weeks before operation were given additional hormones according to a standard schedule. In the other "steroid cases" no coverage was given, but these patients were carefully observed for signs of impending circulatory insufficiency. In the 78 patients treated with cortisone or cortisone-like steroids, this system worked out

satisfactorily. There were no fatal cases, and no serious complications occurred, either in the 48 cases receiving prophylactic cortisone, or in the 30 "steroid cases" in which such treatment was omitted. The prophylactic steroid treatment followed the same standard scheme in all cases, consisting of heavy doses of cortisone. None of these patients showed any signs of delayed wound healing or wound infection.—[Authors' summary.]

1322. **Treatment of Adrenogenital Syndrome: Intramuscular Therapy with Long-acting Prednisosteroids**

J. F. DINGMAN, L. C. MARANAN, and M. C. STAUB. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 1017-1020, June 23, 1962. 9 refs.

Wilkins *et al.* first described the successful suppression of hyperactivity of the adrenal glands by administration of cortisone in 1950 (*Bull. Johns Hopk. Hosp.*, 86, 249; *Abstr. Wld Med.*, 1950, 8, 401). Since then it has been common practice in the treatment of the adrenogenital syndrome to give daily intramuscular injections of cortisone initially, followed by maintenance doses of the drug by mouth. The chief disadvantages have been the difficulty and discomfort of daily intramuscular injections and the incomplete suppression obtained with oral therapy, usually due to irregularity in administration. At the Charity Hospital, New Orleans, 10 women and 6 children were given injections of methylprednisolone acetate and prednisolone trimethylacetate at fortnightly intervals. In the majority of the patients the efficacy of both compounds in suppressing 17-ketosteroid excretion was evaluated. It was found that both drugs resulted in satisfactory suppression of the 17-ketosteroid excretion, but that prednisolone trimethylacetate was more effective than methylprednisolone acetate in improving hirsutism and acne. In some patients it was possible to increase the interval between injections. The authors state that the uniformly smooth suppression of adrenal hyperactivity in these cases was "impressive".

B. M. Ansell

DIABETES MELLITUS

1323. **Causes of Death in 100 Adult Diabetic Patients.** (Les causes de la mort de 100 diabétiques adultes)

M. PLAUCHU, J. DALMAIS, C. PINET, R. TETE, P. A. BRYON, and —. BOURLIER. *Diabète* [Diabète (Le Raincy)] 10, 181-189, June-July, 1962.

The authors have analysed the causes of death in 100 diabetic patients (36 males, 64 females) who died in a hospital at Lyons between 1951 and 1961. The total number of cases of diabetes admitted to the hospital during that period was 652 (311 male, 341 female). The mean age at death in the 100 cases analysed was 64.7 years. Necropsy was performed in 53 cases. In 59 of the patients the primary cause of death was vascular, the largest group being 30 who died from cerebrovascular accidents. Cardiovascular disease accounted for the deaths of 10 patients, 5 of each sex (3 from cardiac infarction, 3 from other acute cardiovascular incidents, and 4 from cardiac failure). Cardiac infarction had also occurred in another 6 diabetic patients who died from other causes; there were thus 9 deaths from cardiac infarction, 6 in women. Circulatory collapse after apparent biochemical recovery from diabetic coma was the cause of death in 5 patients, although they showed no sign of vascu-

lar degeneration. Other causes of death were acute or chronic renal failure (8 cases), peripheral gangrene (5), and vascular accident of uncertain nature (1). Infection, most commonly of the lungs, was responsible for 15 deaths, including 3 from pulmonary tuberculosis. Of 8 patients who died from acute pneumonia, one was an alcoholic. All 5 patients who died in diabetic coma had some other serious complication. One patient died of hypokalaemia persisting after all other biochemical disturbances accompanying a preceding ketosis had been corrected. Hypoglycaemia resulted in the death of 4 patients, one of whom was recovering from diabetic coma. The remaining 16 deaths were attributed to causes unrelated to the diabetes, such as alcoholic cirrhosis (4 cases), alcoholic coma (one case), delirium tremens (one case), and neoplasm (3 cases). The authors compare their findings with those in similar series reported during the last 60 years. Attention is drawn to the emergence over this period of an increasing incidence of deaths from degenerative vascular disorders, accompanying a decreasing incidence of deaths from diabetic coma and pulmonary tuberculosis.

H.-J. B. Galbraith

1324. **Neurological Complications of Diabetes.** (Les complications neurologiques du diabète) B. SCHOTT. *Diabète [Diabète (Le Raincy)]* 10, 191-197, June-July, 1962.

In this paper from the University of Lyons the author points out that few reviews of the neurological complications of diabetes have been written by neurologists (like himself), most being by physicians with a special interest in diabetes. After commenting that usually the neurological manifestations of diabetes are anatomically mixed in type, he outlines a clinico-anatomical classification as follows. (1) Peripheral neuropathies: (a) mononeuritis, especially of branches of the lumbar plexus, such as sciatic, femoral, or obturator neuritis, or meralgia paraesthetica; (b) polyneuritis, usually symmetrical; this is most often a pure sensory neuritis with severe painful paraesthesiae, frequently worse at night, but there is sometimes a mixed sensorimotor disturbance, an associated amyotrophy, or an ataxia, and occasionally a picture identical with that of the Guillain-Barré syndrome. (2) Myelopathies. (3) Cerebral manifestations: (a) local, resembling, for example, cerebral softening or disseminated sclerosis; (b) general, producing epilepsy and disturbances of consciousness or behaviour. (4) Disturbances of the autonomic nervous system: these include trophic changes in the legs, bowel disturbances, impotence, and pupillary changes, sometimes of the Argyll Robertson type.

The physician faced with an unusual complex neuropathy which he finds difficult to explain is advised always to consider the possibility of diabetes. The relative freedom from involvement of the skeletal muscles in diabetes is contrasted with the situation in hyperthyroidism. The author next discusses the aetiological mechanisms of the neurological complications of diabetes. Some such lesions can undoubtedly be attributed to degenerative changes in the vasa nervorum and in the vessels supplying the brain and spinal cord. That the vascular degeneration is hastened by the metabolic consequences of diabetes seems also indubitable. Other manifestations are certainly not vascular in origin, but are due to acute metabolic changes (for example, hypoglycaemia and acidosis). Many of the transient neuro-

logical syndromes, particularly those involving the peripheral neurones, probably also have an underlying biochemical mechanism, although the exact form of this is not known. Finally, the unsuccessful treatment with tolbutamide of 12 non-diabetic patients suffering from disseminated sclerosis, and the use of psychotropic drugs in diabetic patients, are mentioned.

H.-J. B. Galbraith

1325. **Coronary Complications of Diabetes. The Cardiologist's Point of View.** (Les complications coronariennes du diabète sucré. Le point de vue du cardiologue) A. PERRIN, J. NORMAND, G. AIMARD, and R. FROMENT. *Diabète [Diabète (Le Raincy)]* 10, 198-201, June-July, 1962.

The authors describe the features of coronary arterial disease as it affected 14 diabetic patients who died as a result of the cardiac condition at the Hôpital E.-Herriot, Lyons. The data are compared with those for 236 non-diabetic subjects who died from coronary arterial disease during the same 10-year period. Of the 236 non-diabetic patients 90 (39%) were females, while of the 14 diabetics 8 (57%) were females.

The mean age at death was 63½ years in the non-diabetics compared with 57½ years in the diabetics, the difference being largely accounted for by the females, in whom coincident diabetes reduced the mean age at death by over 8 years. Examination of the coronary vasculature by contrast radiography after death demonstrated a similar distribution of lesions in both the diabetics and the non-diabetics. The clinical manifestations of the cardiac ischaemia and the modes of death did not differ in the 2 groups, but in the diabetics the duration of the clinical heart disease before death was less than half that in the non-diabetics.

The authors conclude that not only does coronary arterial disease occur more frequently in diabetics, especially in female diabetics; but it also develops earlier and progresses more rapidly.

H.-J. B. Galbraith

1326. **Immunoelectrophoretic Analysis of Human Insulin-binding Antibody and Its Papain-produced Fragments** J. H. MORSE and J. F. HEREMANS. *Journal of Laboratory and Clinical Medicine [J. Lab. clin. Med.]* 59, 891-897, June, 1962. 3 figs., 13 refs.

The technique of immunoelectrophoresis has aided the classification of immunoglobulins into β_2A -, β_2M -, and γ -globulin. A method utilizing immunoelectrophoresis followed by radioautography was used to show that human insulin-binding antibody is a γ -globulin rather than a β_2A - or β_2M -. This method is applicable for determining the migration of proteins which form soluble complexes with radioactive substances. This method was also applied to papain digests of human insulin-binding antibody. Usually, 3 soluble fragments were produced and the insulin-binding activity was confined to the 2 fractions containing the slowest and intermediate mobilities.—[Authors' summary.]

1327. **Insulin Antibodies in Juvenile Diabetes.** [In English] G. ENGLERSON and S.-B. NILSSON. *Acta paediatrica [Acta paediat. (Uppsala)]* 51, 433-437, July, 1962. 15 refs.

Juvenile diabetes is often easily controlled by insulin for 1 to 3 years and then the condition deteriorates and becomes unstable. The possibility that this deterioration is due to the development of antibodies against insulin has been investigated at the University of Lund, Sweden.

In a system containing tanned sheep erythrocytes, normal rabbit serum as diluent, and amorphous crystalline beef insulin as antigen, serum antibodies were detected in a titre of 1:20 to 1:40 in 5 out of 39 diabetic children; in 3 of the positive cases onset was recent. No positive reactions were found in 100 control subjects. Insulin antibodies are therefore regarded as uncommon in juvenile diabetes. The patients in whom antibodies were found did not show true resistance to insulin or undue instability, so that the antibodies did not appear to be of practical importance. Deterioration of juvenile diabetes is more probably connected with some other type of insulin antagonism.

T. B. Begg

1328. The Relationship between Cardiac Infarction and Diabetes Mellitus, Particularly in Latent Diabetes. (Über die Beziehung zwischen Herzinfarkt und Diabetes mellitus unter besonderer Berücksichtigung des latenten Diabetes). S. BÜCHELE. *Schweizerische medizinische Wochenschrift* [Schweiz. med. Wschr.] 92, 742-746, June 16, 1962. 33 refs.

The author, at the University of Zürich, investigated the relationship between myocardial infarction and manifest or latent diabetes mellitus in 8,665 patients admitted to hospital between January, 1959, and June, 1961. There were 347 cases (4%) of recent myocardial infarction and 625 cases (7.2%) of overt diabetes mellitus. Included in both these figures are 33 patients who had both diabetes and infarction. The incidence of overt diabetes in myocardial infarction was thus 9.5% (33 of 347 patients). The incidence of myocardial infarction in non-diabetic subjects was 3.9% (314 of 8,040) and in diabetic subjects 5.3% (33 of 625). These figures prove, in the author's opinion, that diabetes mellitus predisposes to myocardial infarction, and that there is a statistically significant correlation between the 2 conditions. Of the 347 patients with infarction, the proportion of males to females was 3:1; the average age of the women was slightly higher than that of the men. Of the 33 diabetic patients with infarction, however, 14 were men and 19 women, and the average age at infarction was slightly higher in both, probably because diabetes is more common in higher than in lower age groups. No difference between diabetic and non-diabetic sufferers from infarction was found in respect of severity or mortality.

The author also investigated the incidence of latent diabetes mellitus in 166 patients (145 males, 21 females) with recent myocardial infarction. The examinations were carried out, on an average, 5 weeks, and not less than 3 weeks, after the infarction. In 100 patients a test breakfast containing at least 100 g. of carbohydrate was given; the blood sugar level was estimated in the fasting state and one hour after the meal, and a diagnosis of latent diabetes made if it rose to over 180 mg. per 100 ml. The remaining 66 patients underwent a simple or a double glucose tolerance test by the Staub-Traugott method. Latent diabetes was found in 70 patients (62 men and 8 women)—that is, in 42% of the 166. The author is unable to evaluate the true significance of this high percentage, since no comparative figures are available of latent diabetes mellitus in the general population, and especially in the comparable age group of 60 to 70 years.

The author considers that the reason for the correlation he has established between diabetes mellitus and myocardial infarction must be sought in the mucopolysaccharides, which take part in the formation of vascular connective

tissue. Their synthesis is entirely dependent on glucose availability, which in its turn is influenced by insulin. Diabetic arteriopathy may perhaps be the result of a disturbance of mucopolysaccharide metabolism.

E. S. Wyder

1329. Liver Function in Diabetes Mellitus

R. CAMERINI-DAVALOS, A. MARBLE, and H. MUENCH. *New England Journal of Medicine* [New Engl. J. Med.] 266, 1349-1354, June 28, 1962. 2 figs., 16 refs.

Working at the New England Deaconess Hospital and the Joslin Clinic, Boston, the authors have carried out a number of liver function tests on 398 diabetic patients (194 males and 204 females) under treatment with a restricted diet and with or without insulin, but with no orally administered hypoglycaemic agents, and have compared the results with those obtained in 40 normal subjects. The age distribution of the diabetic patients agreed closely with that of a 25% sample of almost 20,000 patients attending the Joslin Clinic; 90% were over the age of 40 years. Not all the tests were carried out on each patient. No patient with frank liver disease was included, although subjects were not excluded simply on the basis of a palpable liver. Because the distribution of results of the various tests was in most cases asymmetrical, the 90th percentile was used to establish the upper limit of "normal".

Significantly higher 90th percentiles were found in the study group than in the normal group for the "bromsulphalein" retention test (carried out on 354 diabetics), for the serum alkaline-phosphatase level (in 352 diabetics), and for the thymol flocculation test (in 18 diabetics). However, apart from some tendency for bromsulphalein retention to be higher in those who were overweight and in those with elevated serum cholesterol levels, there was no correlation between the abnormal values and such factors as age, sex, body weight, duration or control of the diabetes, or type of treatment. An abnormal value in the bromsulphalein retention test was not correlated with a high serum alkaline-phosphatase level or a high reading in the thymol turbidity test. There was no correlation between abnormal values and recognized associated disease, except that there was a higher than expected proportion of abnormal results in the bromsulphalein retention test in patients with gastro-intestinal disorders, and particularly in those with hepatomegaly. Some of the latter were shown later to have definite liver disease.

A. Gordon Beckett

1330. Chlorpropamide in the Treatment of Diabetes Mellitus

M. I. DRURY and D. KEELAN. *Journal of the Irish Medical Association* [J. Irish med. Ass.] 51, 3-6, July, 1962. 6 refs.

At the Mater Misericordiae Hospital, Dublin, 208 diabetic patients were treated with chlorpropamide for periods varying from 3 to 45 months (mean 16.7 months). The selection of cases was based on the usual criteria. Primary failure occurred in 33 patients (16%), of whom 4 responded to phenformin and 2 to a combination of chlorpropamide and phenformin; 21 were later well controlled by insulin, and in only 9 was the daily requirement in excess of 30 units. Secondary failure occurred in 12 (7% of 145 initial successes) after periods of good control varying from 2 to 22 months; 6 of these had been lax with diet, but in the other 6 there was no factor which suggested that secondary failure could have been foreseen; in 3 patients secondary failure followed closely on an attack of influenza. Good control was

achieved in 63% and moderate control in 11%. Success was higher in those with diabetes of recent onset, in those aged 60 years or more at diagnosis, and in those who were overweight. The relatively high failure rate in all classes of patients suggested that the screening criteria did no more than indicate those in whom success could be attained.

Side-effects of chlorpropamide were few, probably because the initial dose of 500 mg. was reduced as soon as possible. There were 2 rashes, one of which disappeared although the drug was continued, but there was no liver or blood disorder. One patient inadvertently took 1,000 mg. daily for 8 weeks without subjective symptoms and without impairment of blood picture or of liver function tests. In 6 patients intermittent claudication appeared during treatment and one developed severe neuropathy despite excellent control of the diabetes. Foot infection developed in 2 patients, whilst in 7 foot infection already present at the start of therapy became progressive, 2 later requiring amputation. A total of 14 patients died during treatment, but in no case was it considered that death was related to chlorpropamide.

A. Gordon Beckett

1331. Incidence and Causes of Secondary Failure in Treatment with Tolbutamide. Experience with 2,500 Patients Treated up to Five Years

R. A. CAMERINI-DÁVALOS and A. MARBLE. *Journal of the American Medical Association [J. Amer. med. Ass.]* 181, 1-4, July 7, 1962. 6 refs.

A study is reported of 1,965 out of 2,500 diabetic patients given tolbutamide for 4 weeks or longer, with particular reference to secondary failure to respond. Secondary failure was considered to have occurred when, after giving an initial satisfactory response for at least a month, patients later became poorly controlled. Control was defined as "poor" when more than 70% of the blood glucose values were higher than 130 mg. per 100 ml. 3 or more hours after food, 150 mg. 2 hours after food, and 180 mg. one hour after food.

Of the total of 1,965 patients, 432 (22%) experienced secondary failure; 81 (4%) failed during the first year. Of 1,718 treated for not less than 2 years, 162 (9%) failed to respond satisfactorily in the second year; of 1,094 treated for not less than 3 years, 127 (11%) failed during the third year; of 571 treated for not less than 4 years, 51 (9%) failed during the fourth year; and of 147 patients treated for 5 years, 11 (7%) failed to respond in the fifth year. The authors point out that these findings indicate that the incidence of secondary failure does not tend to increase after the third year of treatment with tolbutamide.

Poor initial selection was considered to account for the secondary failure in 110 patients and was "judged to have been made" in the following groups: (1) patients under the age of 40 at onset of the diabetes; (2) those with insulin requirements of over 40 units daily; (3) patients with unstable diabetes and a distinct tendency to ketosis; (4) those in whom the duration of diabetes was more than 10 years; and (5) patients with only fair control during the first month of the trial. In 68 of 432 patients with secondary failure disregard of diet was considered to be responsible and in 163 patients inadequate dosage of tolbutamide—that is, less than 2 g. daily. In 18 patients the secondary failure appeared to be related to metabolic stress; only in the remaining 73 patients was true drug failure thought to be responsible.

Of 127 patients who resumed taking insulin after a period of tolbutamide therapy, the insulin requirement in 74 (58%)

was equal to or lower than that needed before tolbutamide treatment. It was higher than before in 53 (42%) patients, but in 36 of these the increase was less than 20% of the previous total dose of insulin. There is thus no evidence in this group of patients to suggest that the prolonged use of tolbutamide increased the insulin requirement.

Discussing their findings the authors point out that other workers have reported an increased percentage of secondary failures with the passage of time. They consider that some reports may be misleading in that factors other than unresponsiveness to the drug may have contributed to the results. In particular they emphasize the importance of the selection of suitable patients; if the response is only fair during the first month of treatment the chance of a subsequent secondary failure is high. In their view chemical control must be obtained during the initial trial period. Furthermore, the hypoglycaemic action of the sulphonylureas is not great enough to permit dietary indiscretion. Finally the authors state that the cause of the true drug failures, which accounted for only 3.7% of the total, is not clear. "No deterioration in the insulin-producing mechanism appears to have taken place in these patients. It may be that the large insulin requirement seen in some patients after a period of drug treatment is due to ill-defined but frequently observed changes in the course of diabetes and unrelated to oral therapy."

John Lister

1332. A Diabetes Survey

REPORT OF A WORKING PARTY APPOINTED BY THE COLLEGE OF GENERAL PRACTITIONERS. *British Medical Journal [Brit. med. J.]* 1, 1497-1503, June 2, 1962. 7 figs., 13 refs.

The introduction of enzyme tests for glycosuria has greatly simplified the task of urine testing and has made it possible to conduct diabetes surveys on large populations by asking patients to test their own urine. The present paper reports the results of such a survey together with the results of standard oral glucose tolerance tests carried out on those patients who reported a positive result of the enzyme test and also on a sample matched for age and sex drawn from those in the survey population who did not report glycosuria. The survey population consisted of 19,412 patients on the National Health Service lists of 10 general practitioners in the Birmingham area, of whom 18,532 (95.5%) tested their urine. Each patient was given a glucose-oxidase paper strip in a glass vial with silica-gel in the base and sealed by a plastic push-on cap, a questionnaire being attached to the tube. He was instructed to test his urine one hour after his largest meal, record the result, and return the vial to the practitioner by post. All patients in whom the test gave a positive result were asked to attend hospital for interview, examination, and a glucose tolerance test, in which blood glucose levels were determined by Hoffman's method (*J. biol. Chem.*, 1937, 120, 51) using a "technicon autoanalyser" run at 30 readings per hour.

The survey group was found to contain 119 (0.64%) known diabetics, while 493 other patients reported a positive test result. Of the latter, 465 (94%) attended for glucose tolerance test and 127 of these (0.69% of the whole group) were found to give a frankly diabetic glucose tolerance curve. In 70 cases miscellaneous abnormalities were found, such as an initial blood sugar level greater than 110 mg. per 100 ml. but a final level below 120 mg. per 100 ml., a high figure at $\frac{1}{2}$ or 1 hour and $1\frac{1}{2}$ hours but a normal fasting

level, or a normal fasting and 1-hour figure but a final level above 120 mg. per 100 ml. In 100 cases the curve was of the "lag storage" type, in 54 renal glycosuria was present, and 6 cases were unclassifiable owing to probable errors. In 108 cases the patient had reported a positive urine test result, but the result of the glucose tolerance test was normal; this was attributed to misreading of the urine test, or to contamination of the specimen, or to intermittent passage of glucose.

The total of 493 patients reporting glycosuria gives a rate of 2.66%. This figure is low compared with the results of other surveys, but if the 119 known diabetics are included the rate increases to 3.3%. Of 123 patients in the control group, all of whom reported a negative result of the enzyme test, 12 showed a "diabetic" type of abnormality in the glucose tolerance test. Of these 12 patients, 11 were over 50 and none had diabetic symptoms. A further 19 patients over 50 showed a "lag storage" type of curve or miscellaneous abnormality, giving a rate for all types of abnormality of 48% for those over 50 in the control group. The finding in the survey group of 0.64% of known diabetics and 0.69% of previously unknown diabetics is in close agreement with the results of previous surveys, and the postal method of self-testing appears to have been as successful as any other in discovering unknown diabetics. These rates do not represent the total of those giving an abnormal result in the glucose tolerance test, since it was found that about one-fifth of the total population over 50 had a "diabetic" abnormality. Most of these (17.7%) were not discovered by the screening test because they did not manifest glycosuria under the conditions of the test.

In discussing the value of a diabetes detection drive of this type in the light of their results the authors emphasize the frequency with which minor abnormalities of glucose tolerance are discovered. Only follow-up studies will reveal the significance of these deviations from normal and allow a proper assessment of the value of discovering "glucose tolerance test diabetics". On the other hand a detection drive will reveal a number of florid cases of diabetes requiring urgent treatment. Furthermore, if practitioners could be alerted to the higher incidence of diabetes in patients with a family history of the disease, in the obese, and in women who have borne children weighing more than 10 lb. (4.5 kg.), and if the search were restricted to those over 50 years of age, the proportion of florid diabetics discovered "will surely justify such an effort and justify its repetition at regular intervals".

John Lister

1333. Prevalence of Glycosuria and Diabetes Mellitus: a Comprehensive Survey in an Urban Community

J. HARKNESS. *British Medical Journal* [Brit. med. J.] 1, 1503-1507, June 2, 1962. 14 refs.

The author reports the results of a survey the aim of which was to test for glucose a specimen of urine from each of the 6,000 residents of the Essex market and industrial town of Halstead. Specimen bottles were delivered to each house in the town together with an explanatory letter signed by the 4 general practitioners of the town and a form to be completed by the householder. Instructions were given to fill the urine bottles one hour after the main meal of the day. Details of any known diabetics, most of whom did not submit specimens, were obtained on the form, and persons who had recently had a specimen of urine tested for other routine

purposes were generally excused from providing a further specimen. In the case of an infant, the mother was asked to press the end of a "clintix" test paper between the folds of a wet napkin and note the colour change. The urine specimens which were collected were also checked with clintix, and the development of a blue colour was accepted as indicating glycosuria. Most specimens which gave a positive reaction were also tested with "clintest". Those persons giving a positive reaction, apart from known diabetics, were offered a blood sugar examination, and in most cases a modification of the standard glucose tolerance test was performed. A full diet was consumed until 11 p.m. on the night before the test, for which the patient attended fasting at 9.0 a.m. A dose of 50 g. of glucose was given by mouth and venous blood and urine samples tested three-quarters of an hour and 2 hours later.

A total of 5,562 people (2,655 males and 2,907 females) returned urine samples for testing. A further 104 had recently been tested and 137 who failed to supply specimens responded to a subsequent postal survey, testing their own urine with clintix, reporting the result, and returning the test paper. Details of 40 persons reported to be diabetic were also obtained. The total number covered by the survey was thus 5,843, which represents 97.4% of the population of 6,000 (1951 census). Of the 5,562 covered by the house-to-house survey, 148 had glycosuria. Of those participating in the postal survey, 6 returned their clintix noting that it had turned blue. However, only 4 of these strips were blue when examined and in the other 2 cases subsequent postprandial urine specimens were found to be sugar-free. It was assumed that these mildly positive results were due to contamination of the clintix by the patient's fingers.

There were thus 152 cases of glycosuria and 40 reputed cases of diabetes, an incidence of glycosuria of 3.3% in a population of 5,843. Of 150 specimens (none of them from known diabetics) tested with clintest, 64 gave positive and 86 negative results. The glucose tolerance test was performed in 109 cases and the fasting blood sugar level determined in 13. Previously undiagnosed diabetes was discovered in 35 persons (0.57% of the population tested) and details were available of 38 of the 40 previously known cases (0.62%). This shows the incidence of diabetes to be 1.2%. The 35 newly discovered cases of diabetes and the 38 confirmed known cases accounted for 38% of the cases of glycosuria. Of the remainder, 37 were cases of renal glycosuria and 6 of "lag storage" glycosuria, in 34 the result of the glucose tolerance test was normal, 4 were cases of unclassified hyperglycaemia, in 27 confirmatory blood examinations were not carried out, and in 11 others the investigations were insufficiently complete for a firm diagnosis. All the newly discovered cases of diabetes were in subjects over the age of 40, with maximum incidence in the age group 60 to 90 years.

The author points out that his survey supports the view of other workers that there exists one undiagnosed case of diabetes for every known case. It also demonstrates the value of clintix in conducting such surveys and in selecting the cases requiring more detailed examination. He suggests that as a development of his method it should be possible and worth while to carry out mass postal surveys, possibly at regular intervals. Since few significant cases of glycosuria seem to occur in subjects under the age of 20, such surveys might be confined to those over the age of 21, taking the electoral roll of the area selected for study.

John Lister.

The Rheumatic Diseases

1334. Griseofulvin in Acute Gout

S. L. WALLACE and A. W. NISSEN. *New England Journal of Medicine* [New Engl. J. Med.] 266, 1099-1101, May 24, 1962. 2 figs., 10 refs.

In laboratory animals griseofulvin, an antifungal antibiotic with a chemical structure similar to that of colchicine, has been found to cause arrested mitosis in metaphase. Clinically, a good response has been obtained in 14 out of 20 patients given griseofulvin for acute gout at the Jewish Hospital, Brooklyn, New York. Griseofulvin was given by mouth in a total dose varying from 6 to 10 g. according to body size; usually 2 g. was given 4-hourly until the total dose had been taken. Of the 20 patients 15 responded satisfactorily; 2 of the remaining 5 rapidly improved in response to colchicine. There was minimal evidence of toxicity, slight nausea occurring in 3 patients only. It is suggested that griseofulvin probably has a non-specific anti-inflammatory action rather than an action similar to that of colchicine.

B. M. Ansell

1335. The Relationship between Idiopathic Thrombocytopenic Purpura and Systemic Lupus Erythematosus. (Sui rapporti tra porpora piastrinopenica idiopatica e lupus eritematoso sistemico)

G. BALLERINI, S. LA PAGLIA, E. PUNTURIERI, and L. TENZE. *Policlinico, sezione pratica* [Policlinico, Sez. prat.] 69, 777-790, May 28, 1962. 2 figs., bibliography.

The authors, at the University of Ferrara, Italy, have analysed 60 cases of idiopathic thrombocytopenic purpura and 8 cases of systemic lupus erythematosus (S.L.E.). In one case in each group the disease gradually developed into the other, but otherwise little relationship was found. Thrombocytopenia is frequent in S.L.E. and cases of the latter may present the appearance of thrombocytopenic purpura before being recognized. [There is an extensive discussion.]

Arnold Pines

1336. Further Observations on Lupus Erythematosus Associated with Pregnancy

L. B. DONALDSON and R. R. DE ALVAREZ. *American Journal of Obstetrics and Gynecology* [Amer. J. Obstet. Gynec.] 83, 1461-1473, June 1, 1962. 1 fig., 39 refs.

From the University of Washington School of Medicine, Seattle, the authors review 191 pregnancies in 134 patients in whom either systemic or discoid lupus erythematosus (L.E.) was diagnosed. Of these, 49 pregnancies in 22 patients were studied personally or through the records of the Seattle hospitals, whereas information concerning the remainder was obtained as a result of a questionnaire sent to the members of District VIII of the American College of Obstetricians and Gynecologists.

The cases were divided into 3 clinical groups: acute and subacute systemic, chronic systemic, and discoid L.E. In approximately two-thirds of the patients suffering from acute, subacute, or chronic systemic L.E., pregnancy had no apparent effect upon the course of the disease, but in approximately one-sixth the course was aggravated. The

effect of acute L.E. upon the pregnancy was more marked than was the case with chronic L.E., and in the patients with discoid L.E. the pregnancy differed little from that in normal subjects. Of the patients with acute L.E., 25% had toxæmia of pregnancy, while in 12% stillbirth and in 10% spontaneous abortion occurred. The total foetal wastage was 25%. After toxæmia, renal disease, due either to nephritis or to nephrosis, was the second most frequent cause of complications. Therapeutic abortion was attempted in 12 cases of acute systemic L.E.; 3 of the patients died. There were 9 deaths in the whole series, 8 patients dying post partum. It is suggested that termination of the pregnancy may have aggravated the condition. It is further suggested that this may be due to the removal of the suppressive influence of the corticoids produced during pregnancy, and in consequence the authors recommend the continued use of heavy doses of steroids, not only during pregnancy, but also for several weeks after delivery.

R. E. Tunbridge

1337. High Dosage Steroid Therapy for Systemic Lupus Erythematosus

E. L. DUBOIS. *Arthritis and Rheumatism* [Arthr. and Rheum.] 5, 250-260, June, 1962. 4 figs., 14 refs.

In this paper from the University of Southern California School of Medicine and the County Hospital, Los Angeles, 4 cases of systemic lupus erythematosus are described [3 in convincing detail] in which massive dosages of corticosteroids were given. Cortisone in a dosage up to 2.3 g. daily appeared to control the disease in 3 patients although vertebral collapse and psychoses were seen. In the remaining case corticosteroids in a dosage up to 3.6 g. daily did not prevent death within 3 months. This patient had had lupus erythematosus for 11 years and an exacerbation for 6 months. The author emphasizes that a "Cushingoid" appearance is usually noted, even with very large dosage, only when remission has been induced; the dosage is therefore increased until the features of the Cushing syndrome are apparent. Central nervous system involvement was thought to be due to vasculitis in the brain or spinal cord or, in 2 cases in the series, to water intoxication. In one case there was a remission of 8 years' duration, the patient being maintained on small (25-mg.) doses. This case was remarkable for the "complete architectural recovery of the vertebrae" from "advanced osteoporosis with multiple compression fractures".

E. G. L. Bywaters

1338. Physical Activities and Rheumatic Heart Disease in Asymptomatic Patients

A. R. FEINSTEIN, H. TAUBE, R. CAVALIERI, S. C. SCHULTZ, and L. KRYLE. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 1028-1031, June 23, 1962. 10 refs.

Working at the Irvington House After-Care Clinic, New York University School of Medicine, the authors have studied the effect of physical activity on the progress of rheumatic heart disease in 216 patients who were followed up for an average of 21 years after an attack of rheumatic fever. In 26 (12%) of these patients the "objective cardiac

status", evaluated by means of standard criteria for the findings on auscultation and fluoroscopy, deteriorated, while in 50 (23%) there was improvement. In 140 cases (65%) there appeared to have been no change.

These percentages remained essentially unchanged when the findings were analysed according to the enforcement or absence of restrictions upon the patients' physical activities, during their school life, at home, or in later life after leaving school. The results suggest strongly that no really useful medical purpose is served by many of the physical and other restrictions which are often imposed upon patients who are known to have suffered from rheumatic fever but who present no symptoms, whether or not they have developed any cardiac lesion. Such restrictions do not appear to influence cardiac deterioration either favourably or otherwise. Moreover, it was found in this series that adverse psychological reactions developed in 34% of the 141 patients whose school activities were restricted, but in only 6% of the 75 whose activities were not interfered with. *W. S. C. Copeman*

1339. Further Results of the Prophylaxis of Relapse in Acute Rheumatism in the Children's Hospital, München-Schwabing. (Weitere Ergebnisse der Rezidivprophylaxe des rheumatischen Fiebers im Kinderkrankenhaus München-Schwabing)

F. LOEBER, W. EICHLSEDER, and D. STUMPF. *Monatsschrift für Kinderheilkunde* [Möchr. Kinderheilk.] 110, 315-318, June, 1962. 1 fig., 13 refs.

The prolonged use of prophylactic penicillin treatment for children who had had an attack of rheumatic fever was not introduced into the practice of Schwabing Children's Hospital, Munich, until 1955. By then many favourable reports had been published from American sources. After introduction of the measure, the incidence of relapses fell steeply and among 64 cases treated by this method between 1955 and 1961 only one relapse was seen. This was contrasted with a control group of 60 other patients who were not given such prophylaxis [but who were not strictly comparable controls] and in whom 7 relapses were noted. Finally, in 15 children who were treated with penicillin after an attack of rheumatic fever only if they had tonsillitis, 3 severe relapses were observed. [A belated discovery.]

John Lorber

CHRONIC RHEUMATISM

1340. Serological Reactions and the Etiology of Rheumatoid Arthritis. (Part II.) [In English]

K. E. THULIN. *Acta rheumatologica Scandinavica* [Acta rheum. scand.] 8, 3-9, 1962. 1 fig., 7 refs.

The author, working at the University of Lund, Sweden, studied the agglutination of autoclaved Group-A β -haemolytic streptococci by the sera of patients with rheumatoid arthritis. This agglutination was inhibited by Cohn Fraction I of retroplacental serum. This was demonstrated by incubating the streptococci with the Cohn fraction at room temperature followed by washing and addition of serum. Incubation at 37° C. or with Cohn Fraction I from normal serum caused little inhibition. Agglutination of live and autoclaved streptococci was inhibited by hyaluronic acid of mammalian origin and autoclaved synovial material. These inhibition studies suggest that antibodies against mesenchymal tissue occur in rheumatoid arthritis and raise the ques-

tion whether the sera contain antibody against some part of the hyaluronic acid molecule. In the light of these findings the author suggests that in rheumatoid arthritis a primary abnormality of the enzyme systems involved in the metabolism of mesenchymal tissue gives rise to degradation products which are antigenic. Tissue damage then results both from the altered enzyme activity and from autoimmunity. *G. L. Asherson*

1341. Comparison between Serological Reactions in Hyaluronidase Treated Joint Exudate and Whole Sera from Patients with Rheumatoid Arthritis. [In English]

K. E. THULIN. *Acta rheumatologica Scandinavica* [Acta rheum. scand.] 8, 10-21, 1962. 6 refs.

The author has previously shown that the factors in the serum of patients with rheumatoid arthritis which agglutinate live and autoclaved streptococci are different from the rheumatoid (haemagglutinating) factor which agglutinates sensitized sheep erythrocytes. He has now studied the distribution of these factors in joint fluid and serum. Joint fluid was obtained from 45 patients with joint injuries, sera from 100 healthy subjects, and joint fluid and serum from 62 patients with active rheumatoid arthritis. The streptococcal agglutination tests gave negative results in all joint fluids from patients with joint injury, even after treatment of the fluid with hyaluronidase. The rheumatoid factor occurred in a titre of 1:20 in 3 patients. After treatment with hyaluronidase, 21 fluids showed a titre of 1:20 or higher. Titres of 1:20 of the rheumatoid factor and agglutinating factors for streptococci were found in 9 to 15% of sera. Only 3 to 4% showed titres of 1:40, and no higher titres were found. On the basis of these figures streptococcal agglutination in joint fluid was regarded as positive if the titre was above 1:20 and in serum if it was above 1:40. For rheumatoid factor the limits were respectively 1:80 and 1:40.

Of the sera of patients with rheumatoid arthritis, a positive reaction to the streptococcal agglutination test occurred in 40 to 50% and to the haemagglutination test in about 70%. The figures for joint fluid were 20% and 35%, but these rose to between 65% and 74% after treatment with hyaluronidase. When the patients were classified according to the severity of the radiological changes in the joints, it was found that the incidence of the haemagglutinating factor and the antibody to live streptococci increased with the severity of the disease. Antibody to the autoclaved streptococci was not associated with severity. However, the incidence of positive reactions in joint fluid increased with the severity of the disease for all 3 factors. In cases observed over several years, the haemagglutination factor usually appeared before the streptococcal agglutination factor and the streptococcal agglutination factor fluctuated, perhaps because of variation in the level of (hypothetical) serum inhibitors. Of the sera from patients with rheumatoid arthritis, 31% agglutinated human erythrocytes coated with anti-Rh antibody. None of the joint fluids were active.

The author draws attention to the higher incidence of positive streptococcal agglutination reactions in the joint fluid as compared with the serum, and suggests that the joint factors may be different from the serum factors and that the lower incidence in serum may be related to inhibitors. He concludes that the haemagglutination factor is distinct from the streptococcal agglutination factor and presumably has different clinical significance. *G. L. Asherson*

1342. **Further Investigation of the Relationship between the Streptococcal Agglutination Reactions and Other Serological Reactions in Rheumatoid Arthritis.** [In English]. K. E. THULIN. *Acta rheumatologica Scandinavica* [*Acta rheum. scand.*] 8, 22-30, 1962. 9 refs.

This third paper [see Abstracts 1340 and 1341] provides further evidence for the distinct nature of the streptococcal agglutinating factors and the rheumatoid factor. Absorption with live streptococci of hyaluronidase-treated joint exudate from a patient with rheumatoid arthritis removed the streptococcal agglutinating factors but left the rheumatoid factor unaffected. Absorption with autoclaved streptococci removed only the antibody to autoclaved streptococci. Absorption of 6 sera with heated human γ -globulin removed the rheumatoid factor but left the streptococcal agglutinating factors almost unaltered. When the sera of 6 patients with rheumatoid arthritis were dialysed against distilled water the rheumatoid-factor activity was found entirely in the euglobulin precipitate, while the streptococcal agglutinating factors were found only in the supernatant. When 6 joint exudates treated with hyaluronidase were fractionated, the rheumatoid-factor activity was found in both the euglobulin precipitate and the supernatant, but no streptococcal agglutinating activity was recovered.

The author concludes that the streptococcal agglutinating factors and the rheumatoid factor react with distinct antigens and differ in their physicochemical properties.

G. L. Asherson

1343. **Rheumatoid Heart Disease: a Study of the Incidence and Nature of Cardiac Lesions in Rheumatoid Arthritis** E. S. CATHCART and D. H. SPODICK. *New England Journal of Medicine* [*New Engl. J. Med.*] 266, 959-964, May 10, 1962. 16 refs.

The authors, working at the Lemuel Shattuck Hospital, Boston, have studied the nature and incidence of heart disease in rheumatoid arthritis. The records of 254 patients (51 male and 203 female), all of whom had typical rheumatoid arthritis as judged by accepted criteria, were investigated. For comparison the records of 254 patients matched for age and sex were chosen at random; cases of primary heart disease or disease of the lungs, kidney, or cerebral vascular system associated with cardiac failure were excluded from the control series. Of the patients with rheumatoid arthritis, 88 (34.8%) had signs of organic heart disease compared with 37 (14.6%) of the controls.

The types of heart disease identified were classified under 4 headings. Group A consisted of patients with evidence of hypertension—defined as a blood pressure of not less than 160 mm. Hg systolic or 90 mm. Hg diastolic—and radiological evidence of left ventricular enlargement. There were 20 such patients (7.9%) in the study group and 19 (7.5%) in the control group. Group B included cases of coronary arterial disease as evidenced by angina pectoris or electrocardiographic (ECG) changes. There were 18 (7.1%) cases in the study group and 4 (1.4%) in the control group. In addition, it was estimated that a further 18 (7.1%) of the study group had probable evidence—including ECG changes—of coronary disease compared with 8 (3.2%) in the control group. Group C consisted of those patients with cor pulmonale or amyloidosis; there were 3 in the study group and 2 in the control group. Group D consisted of cases of indeterminate heart disease and included

patients with unusual cardiac findings such as ECG or radiological evidence of enlargement of the left or right atrium or of the right ventricle, diastolic murmurs, and unexplained disorders of conduction. There were 29 such patients (11.4%) in the study group and only 4 (1.6%) in the control group. Necropsy was performed on 15 of the study group (including 5 of Group D). Pericarditis was observed in 6 of these cases and in 7 instances rheumatoid lesions were found in the heart. In all of the 5 patients in Group D rheumatoid lesions were present in the heart.

The authors point out that the higher incidence of heart disease among the patients with rheumatoid arthritis is statistically significant. Commenting on the high incidence of indeterminate lesions, they consider that the necropsy findings in the 5 cases so far examined are highly significant and leave little doubt that these indeterminate lesions are due to rheumatoid and not to rheumatic heart disease.

William Hughes

1344. **Acute Pericarditis: with Subsequent Clinical Rheumatoid Arthritis**

L. A. GROSSMAN, H. J. KAPLAN, F. D. OWNBY, and M. GROSSMAN. *Archives of Internal Medicine* [*Arch. intern. Med.*] 109, 665-672, June, 1962. 8 figs., 12 refs.

The authors review the literature concerning the occurrence of cardiac lesions in rheumatoid arthritis and describe 3 cases of pericarditis complicating the disease which were seen at Vanderbilt University Hospital, Nashville, Tennessee. The first was in a 17-year-old male whose initial symptoms were chest pain and in whom there were positive electrocardiographic (ECG) signs of acute pericarditis. The leucocyte count was 11,200 per c.mm., the C-reactive protein test gave a 3+ positive result, and the serum antistreptolysin-O (ASO) titre was less than 50 Todd units. There was a swinging temperature up to 103° F. (39.4° C.), which gradually decreased over 3 weeks. Thoracentesis yielded 150 ml. of inflammatory exudate. Rapid improvement followed treatment with isoniazid, but a relapse occurred 4 months later, when an exploratory thoracotomy revealed the presence of pericarditis. Biopsy of the pericardium, pleura, and left lung showed acute and chronic types of inflammatory cellular exudate with occasional giant cells. No tubercle bacilli were found. Fever continued in spite of isoniazid therapy, but abated after steroid therapy. The ASO titre was increased to 500 Todd units and remained high for the next 2 years. Spindling of several metacarpophalangeal joints and arthritis of the right elbow-joint developed, but the patient remained ambulant. The second case was that of a 47-year-old male whose illness started with an influenzal type of fever and signs of a pleural effusion on the left side. Positive ECG and radiological signs of pericarditis with effusion were observed and 400 ml. of fluid was aspirated from the chest. There was no leucocytosis and lupus erythematosus (L.E.) cells were not found. The pericardial effusion subsided after the institution of steroid therapy. One month after the patient's discharge from hospital he relapsed and was readmitted. After exploratory thoracotomy, sections of the lung, pleura, and pericardium revealed no specific changes. Cultures yielded no tubercle bacilli, and no L.E. cells were demonstrated. He subsequently developed nodules about the elbow and pain in the spine, shoulders, elbows, and interphalangeal joints, with some swelling about the proximal interphalangeal joints.

The third case was that of a 53-year-old woman who developed fever and leucocytosis with positive radiological and ECG evidence of pericarditis. No L.E. cells were found in the blood, and blood culture was negative. On thoracentesis 200 ml. of sterile, straw-coloured fluid was withdrawn. The condition improved and the patient was discharged but relapsed after 4 months, enlargement of the interphalangeal joints and knee-joints developing.

In summarizing their findings the authors note that pericarditis with effusion was followed after an interval of several months in these 3 cases by clinical manifestations of rheumatoid arthritis. They point out, however, that the cases are still under observation and it may be that in time they will develop other forms of collagen disease.

William Hughes

1345. The Reaction of Rheumatoid Factor and Complement with γ -Globulin Coated Latex

G. C. BERNHARD, W. CHENG, and D. W. TALMAGE. *Journal of Immunology* [J. Immunol.] 88, 750-762, June, 1962. 7 figs., 29 refs.

The authors, from the University of Colorado, Denver, report their attempts to elucidate the nature of the factor in rheumatoid arthritic serum which causes fixation of γ -globulin-coated latex. The basis of agglutinating reactions in rheumatoid arthritis is a particle coated with aggregated γ -globulin molecules. The authors have modified the latex fixation test to measure photometrically the optical density of the supernatant, and thus provide objective quantitative data over a wide range of dilutions of rheumatoid arthritic serum. It has been shown that γ -globulin aggregated by heat or by antigen-antibody complexes will adsorb the rheumatoid factor. By incubating Cohn Fraction II (a commercial preparation of lyophilized human γ -globulin), human γ -globulin (HGG), and bovine serum albumin (BSA) successively with latex suspension, the authors were able to show that the protein-latex bond was stable. Once a protein was adsorbed it could not be removed by repeated washing or eluted by dilute sodium hydroxide. One protein will not displace another, nor is there any evidence of exchange when excess protein of the same type is present. Thus when the authors added a mixture of ^{131}I -labelled BSA and unlabelled BSA, and then a large excess of BSA, there was no exchange of protein. Although the protein-latex bond is stable, further protein can be adsorbed from a heterogeneous mixture such as Cohn Fraction II and HGG. The authors were able to increase the amount of nitrogen taken up from 4.9 to 12.4 μg . per mg. latex in these circumstances. A flat agglutination curve is obtained by adding latex coated with unheated Cohn Fraction II to rheumatoid serum, but precipitation occurs, yielding a sigmoid curve, when heated Cohn Fraction II is used. Pooled eluates of the γ -globulin fraction from curtain electrophoresis of human serum (CE-HGG) produced sigmoid curves whether heated or not, and these were further to the right than the heated Cohn Fraction II curve, suggesting that CE-HGG was a better source of "reactant". Fresh human serum (NHS) produced a striking inhibition of agglutination, but heated NHS had no such effect. Heating the mixture of fresh NHS and latex before the addition of rheumatoid serum did not reverse the inhibition. This suggests that the inhibiting agent is reacting with the coated latex and not with the rheumatoid serum. Guinea-pig serum had the same effect as NHS in this respect. Latex coated with BSA

did not fix complement. Since free CE-HGG does not fix complement and latex coated with CE-HGG does, it is probable that the γ -globulin molecules are aggregated on to the surface of the latex. Excess reactant globulin in solution does not inhibit agglutination by rheumatoid serum, in contrast to what happens in many antigen-antibody agglutination systems. A prozone phenomenon in agglutination was produced by adding latex coated with HGG or CE-HGG to serial dilutions of a fresh rheumatoid serum. The prozone phenomenon was obliterated by adding heated Cohn Fraction II to CE-HGG-coated latex before incubation with the rheumatoid serum. The authors interpret these findings as showing that complement and rheumatoid factor are attached to similar sites on aggregated γ -globulin. The fact that γ -globulin-coated latex can fix complement is additional evidence in this direction. There are, however, minor differences in specificity between the two factors.

William Hughes

1346. Treatment of Osteo-arthritis of the Hip by Interstitial Cobalt 60 Irradiation

P. N. ROBSON and P. J. VAN MIERT. *British Journal of Surgery* [Brit. J. Surg.] 49, 624-636, May, 1962. 23 figs., 16 refs.

The authors' method of treatment is based on the view that much of the pain in osteoarthritis of the hip is due to congestion and oedema in the cancellous bone of the femoral head and neck. The evidence for this view is stated, and the vascular anatomy within the bone is described. Irradiation in suitable doses can reduce vascularity, and interstitial irradiation from a source centrally placed in the femoral head is the only practical way of achieving the required dose. Attempts to relieve pain by conventional irradiation from external sources have not been conspicuously successful. An isodose diagram shows how insertion of a 2-mm. diameter radioactive cobalt (^{60}Co) source of 55 to 90 mc. centrally in the femoral head enables a very high central dose, falling off to no more than 1,400 r. at the surface of the head, to be given in 5 to 10 hours. This dose has proved safe and free from complications. The ^{60}Co is inserted through a drill hole in the manner of a Smith-Petersen pin. Extreme accuracy of centering is necessary and the procedure is described in detail. It is carried out under careful x-ray control, and the dose rate is calculated from the final radiograph. There have been no operative deaths and no cases of wound sepsis in the series described.

The report is based on the first 100 cases treated, 95 of them at least 2 years ago, at the Royal Victoria Infirmary, Newcastle upon Tyne. The average age of the patients (38 male and 62 female) was 62 and many were in poor general condition. Severe pain, but not limitation of movement alone, was considered to be a suitable indication. The cases were divided into three groups according to the degree of severity, and the results were assessed as: (1) completely satisfactory relief of pain; (2) substantial relief of pain, but pain still felt on moderate activity; and (3) slight or no improvement. After 2 years the results in 60% of the patients fell into Group 1 and in only 27% into Group 3. The results were best in the younger patients and in those in whom the disease was less advanced. Comparing their results with those in a published series treated by simple forage—that is, drilling of the bone to reduce tension—the authors find that the effects of irradiation are better and appear to last longer.

E. Stanley Lee

Neurology and Neurosurgery

1347. **A New Method of Rheoencephalography and Its Results Up to Date.** (Eine neue Methode der Rheoencephalographie und ihre bisherigen Ergebnisse) H. LECHNER and H. RODLER. *Wiener medizinische Wochenschrift* [Wien. med. Wschr.] 112, 435-438, June 2, 1962. 6 figs., 6 refs.

The authors, from the University of Graz, describe a new method of rheoencephalography. A generator delivers a constant 9-kilohertz current which is connected to the scalp by two electrodes. The current produces potential changes synchronous with the pulse which can be recorded from the scalp surface. When the technique was tested in experimental animals and in patients it was found that the rheoencephalogram (REG) was capable of registering changes in cerebral blood flow. The changes occurred more promptly than electroencephalographic (EEG) changes, and no direct relationship with the EEG was found. The amplitude of the curves in the REG was reduced by a fall in blood flow. Nitrogen and carbon dioxide inhalation and jugular compression increased the amplitude of the REG waves, while breathing pure oxygen resulted in a decrease. External carotid circulation had no effect on the REG. Compression of one carotid artery in patients with poor collateral circulation reduced the amplitude of the REG on the same side. No change was seen in normal subjects on carotid compression.

The authors suggest that this new method may be of value in the study of the cerebral circulation.

H. S. Schutta

1348. **Clinico-radiological Observations in Strümpell's Familial Spastic Paraplegia.** (Клинико-рентгенологические наблюдения при семейном спастическом парапарезе Штрюмпелля)

A. A. BAZENOVA and V. JA. NERETIN. *Журнал Невропатологии и Психиатрии* [Zh. Nevropat. Psikhiat.] 62, 661-665, No. 5, 1962. 4 figs., 7 refs.

The authors describe 4 patients with hereditary spastic paraplegia, of whom 3 were siblings and one belonged to a family in which the father and 2 siblings, now dead, were said to have had the disease. All 4 patients became affected in the late teens or early twenties by spastic weakness which developed over the course of a few years into severe spastic paraplegia with pyramidal signs. There was no disturbance of sensation or of the functions of the pelvic organs. Slight lower-thoracic kyphoscoliosis was present in 3 of the patients and pronounced lower-thoracic kyphosis in one. In all 4 cases the following features were seen in the radiographs of the thoracic spine. The outlines of the epiphyses were clear, undulating, irregularly triangular, and separated by a cartilaginous layer from the body of the vertebrae. Sclerosis and linear striae were present in the laminae. Large exostoses grew from the anterior edges of the vertebrae. Development of the vertebrae was retarded and they had failed to gain their biconcave form, remaining instead rectangular or wedge-shaped. There was delayed development of the intervertebral space, which was irregularly

widened or narrowed. In some cases the inferior surfaces of the vertebrae were segmented. These features are said to be similar to but not identical with those of Scheuermann's disease, and the authors regard them as dystrophic bone changes consequent on the disease of the central nervous system. Their presence may help in the diagnosis of early or isolated cases of hereditary spastic paraplegia.

G. P. McGovern

1349. **Value of Nerve-excitability Measurements in Prognosis of Facial Palsy**

E. D. R. CAMPBELL, R. P. HICKEY, K. H. NIXON, and A. T. RICHARDSON. *British Medical Journal* [Brit. med. J.] 2, 7-10, July 7, 1962. 1 fig., 8 refs.

In cases of facial palsy it is difficult to be sure in the early stages whether there is a physiological block or degeneration of the nerve fibres. The authors, working at the Royal Free Hospital, London, have investigated this problem by stimulation of the facial nerve at a point below the mastoid process and behind the angle of the jaw. A small active electrode was used, with a large inactive electrode on the back of the neck, the findings being compared with those on stimulation of the opposite facial nerve. Studies were made on 197 patients with peripheral facial palsies of varied aetiology, the most common being Bell's palsy. In patients in whom nerve degeneration had occurred and in whom recovery was unlikely to start for 3 months or more, evidence of diminished or absent excitability in the facial nerve could normally be demonstrated within 72 hours of onset. This is some days earlier than denervation can be demonstrated by means of the strength-duration curve or electromyography. In 9 patients nerve excitability was normal within the first few days, but was lost between the 7th and 21st days, and the explanation for this is not at present clear. The authors consider this a valuable method of distinguishing between physiological block and degeneration of the facial nerve within 72 hours of the onset of a facial palsy.

[This is clearly a valuable method of estimating prognosis in facial palsy and, as the authors point out, was foreshadowed by Duchenne in 1872, but has apparently been neglected since then.]

J. W. Aldren Turner

1350. **Therapeutic Trials in Multiple Sclerosis: Final Report on Effects of Intrathecal Injection of Tuberculin (P.P.D.)** H. G. MILLER, D. J. NEWELL, A. R. RIDLEY, and K. SCHAPIRA. *British Medical Journal* [Brit. med. J.] 1, 1726-1728, June 23, 1962. 8 refs.

From the Royal Victoria Infirmary and the Medical School, Newcastle upon Tyne, the authors report the results of a controlled trial of tuberculin (P.P.D.) given intrathecally in the treatment of disseminated sclerosis. The 90 patients included in the trial were divided at random into three groups, one of which was treated by repeated lumbar puncture only, the second by the repeated intrathecal injection of saline, and the third by intrathecal injection of P.P.D. on two occasions, each injection causing a rise of over 100 mg. per 100 ml. in the protein content of the cerebrospinal fluid.

Disability was assessed in seven grades, and the patients were reviewed and their progress assessed by an observer who was unaware of the treatment group to which the patients belonged. The findings lend no support to the suggestion that intrathecal P.P.D. has a beneficial effect on the course of this disease. Indeed, it appeared to induce an increased number of exacerbations during the succeeding one to 3 years. The reaction to this form of treatment was always unpleasant and sometimes alarming.

[This work would seem finally to confirm the condemnation of P.P.D. as a form of treatment. It seems now to have been abandoned or frankly discredited by every British neurologist who has used it—with the exception of its inventors.]

Hugh Garland

1351. **Prolonged Treatment of Disseminated Sclerosis with Tolbutamide.** (Versuch einer Langzeitbehandlung der Multiplen Sklerose mit Tolbutamid)

U. VOGR. *Medizinische Klinik [Med. Klin.]* 57, 1016–1017, June 8, 1962. 7 refs.

At the Auguste-Victoria Hospital, Berlin, the author treated 19 patients suffering from disseminated sclerosis with 1.5 g. of tolbutamide a day for up to 10 months. In 4 patients temporary improvement occurred, but was followed by fresh exacerbation of the disease. In the remaining patients no modification in the course of the disease was observed. There was no correlation between changes in carbohydrate metabolism and the symptomatology.

H. S. Schutta

1352. **Functional State of the Adrenal Glands in Patients with Myasthenia Gravis.** (К вопросу о функциональном состоянии коры надпочечников у больных миастенией)

V. M. PRIHOZHAN. *Проблемы Эндокринологии и Гормонотерапии [Probl. Endokr. Gormonoter.]* 8, 86–88, May–June, 1962. 8 refs.

The close relationship between myasthenia gravis and hypertrophy of the thymus has led to the suggestion that adrenocortical insufficiency may play a part in the pathology of this disease. This role could be primary, as suggested by Bonoscow and Milzner, or it could be secondary to diencephalic (hypothalamic) dysfunction. The present author describes experiments carried out to elucidate this problem. Adrenal function was measured in 52 cases of myasthenia gravis by estimation of the urinary output of 17-oxycorticosteroids, 17-ketosteroids, and dehydro-iso-androsterone. The ages of the 52 patients (15 men and 37 women) ranged from 10 to 57 years. The condition was mild in 12 cases, of medium severity in 29, and severe in 11. The excretion of 17-ketosteroids was normal in all except 6, in whom it was raised. (In these 6 patients irradiation of the thymus had previously been carried out.) In all except 3 the excretion of dehydro-iso-androsterone was normal; in the remaining 3 it was raised. The excretion of 17-oxycorticosteroids, which was estimated in 50 patients, was reduced in 18, at the lower limit of normal in 12, and normal in 20. Corticotrophin (ACTH) was given to 33 patients in a dosage of 20 to 40 units. In 27 there was no increase in excretion of corticosteroid metabolites in the urine; in 23 there was no lymphogenic reaction and in 13 no eosinopenic reaction; in 21 there was no positive swing in the potassium:sodium coefficient. On repeated dosage with ACTH, however, increase in adrenal function was shown by all these tests.

It is therefore concluded that in myasthenia gravis there is no primary dysfunction of the adrenal glands, but that there is a secondary insufficiency due to disturbance of the hypothalamo-hypophyso-adrenal relationship. It is probable that hypertrophy or other disease of the thymus gland results from this.

L. Firman-Edwards

1353. **The Carpal Tunnel Syndrome: Investigation and Assessment of Treatment**

E. D. R. CAMPBELL. *Proceedings of the Royal Society of Medicine [Proc. roy. Soc. Med.]* 55, 401–405, May, 1962. 5 figs., 11 refs.

Both motor and sensory nerve conduction times in the median and ulnar nerves were estimated in 96 patients at the Royal Free Hospital, London, who complained of acroparaesthesiae in the hands. In 41 of the 96 patients the nerve conduction times were normal; in 2 of these 41 the diagnosis of the carpal-tunnel syndrome seemed certain clinically, but in neither case had symptoms been present for more than 3 weeks. In the remaining 39 patients in this group some other cause for the acroparaesthesiae was found. Abnormalities of either motor or sensory nerve conduction times were present in 55 patients; all of whom were considered to have a carpal-tunnel syndrome.

The author considers that these nerve conduction studies serve accurately to differentiate the carpal-tunnel syndrome from other causes of acroparaesthesia.

J. W. Aldren Turner

BRAIN AND MENINGES

1354. **Chorea Minor.** (La "corea minor")

C. LAMBERTINI and A. BRUNELLI. *Minerva pediatrica [Minerva pediat.]* 14, 517–531, April 21 [received June], 1962. 2 figs., bibliography.

The authors review the case histories of 20 patients with Sydenham's chorea admitted to the Institute of Clinical Paediatrics of the University of Milan between 1954 and 1960. The case histories are accompanied by the findings obtained by electrocardiography, phonocardiography, and electroencephalography, and the results of laboratory investigations such as plasma protein electrophoresis and determination of the erythrocyte sedimentation rate and the antistreptolysin titre. These data are viewed in the light of the various conclusions published in the literature (here briefly reviewed) concerning the aetiology and pathogenesis of chorea minor. Treatment and prognosis in the authors' own material are discussed. Treatment was of two main types—anti-infective, including administration of antibiotics, and anti-inflammatory, including corticotrophin (ACTH) and corticosteroids. In addition, non-specific therapy (sedation, vitamin supplements, and administration of liquor arsenicalis and thiouracil) was employed. There seems to have been no significant difference in the results of the various forms of treatment, and all the patients recovered. Follow-up examination of 9 patients at intervals ranging from 5 months to 7 years after the acute illness showed no evidence of recurrence.

Discussing the relationship of chorea to rheumatism the authors conclude that it is more profitable to speak of an association between the two conditions, possibly with an underlying constitutional predisposition which embraces both, than of a causal relationship. They conclude that

the efficacy of antirheumatic treatment in chorea depends on the presence of a substrate of active rheumatism.

J. B. Stanton

1355. **Cataplexy on Awakening and Falling Asleep.** (О катаплексии пробуждения и засыпания)
V. S. LOVZIN. *Журнал Невропатологии и Психиатрии* [Zh. Nevropat. Psikhiat.] 62, 808-814, No. 6, 1962. 1 fig., 26 refs.

The author reports on 5 young men who suffered from attacks of cataplexy on falling asleep or awakening. During the attacks, which were accompanied by a sensation of intense apprehension, the patient remained fully aware of his surroundings but was practically unable to make any movement. He usually contrived to be "wakened" by calling to a relative to apply some strong sensory stimulus. Common associated symptoms were headache, difficulty in falling asleep, light sleep and nightmares or, alternatively, unusually deep, dreamless sleep. One patient also suffered from narcolepsy. The second patient was observed during several attacks. These were accompanied by flushing of the face, conjunctival injection, diminution of pupillary reflexes, and absence of the corneal reflex. Although the patient could afterwards describe all that happened during the attacks, these could be interrupted only by energetic shaking. In the third patient the attacks began 2 months after a head injury sustained at the age of 10. On examination there were signs of a left upper motor neurone lesion, and air encephalography showed marked dilatation of the third ventricle. The fourth patient was an emotionally unstable, explosively aggressive psychopath. The fifth patient had 8 relatives of both sexes, belonging to 3 generations, in whom the syndrome was present in identical form, "explosiveness" and lack of self-control being characteristic features. The syndrome was inherited in a dominant manner.

The author discusses the physiopathological mechanism of these cases in terms of inertness and prolonged localization of cortical inhibition, perhaps resulting from disturbance of the regulatory function of the reticular formation. He regards the cases as representing an independent clinical syndrome of multiple causation.

G. P. McGovern

1356. **Subcortical Arteriosclerotic Encephalopathy: Review of the Literature on the So-called Binswanger's Disease and Presentation of Two Cases**

J. OLSZEWSKI. *World Neurology* [Wld Neurol.] 3, 359-375, May [received Aug.], 1962. 11 figs., 29 refs.

In 1894 Binswanger (*Berl. klin. Wschr.*, 31, 1103) described 8 patients suffering from a progressive form of presenile dementia with focal neurological signs, a condition to which he gave the name "encephalitis subcorticalis chronica progressiva" and which has subsequently become known as Binswanger's disease. The characteristic pathological feature was said to be arteriosclerosis of the cerebral vessels with focal lesions confined to the white matter, the cortex being spared. In the present paper the literature of this condition is reviewed and the conclusion is reached that a form of cerebral arteriosclerosis does exist in which the vessels of the white matter and the subcortical grey matter are predominantly affected. The term "subcortical arteriosclerotic encephalopathy (Binswanger type)" is proposed for this condition. The author has studied 2 examples in the Department of Pathology of the University of Toronto.

The pathological features included diffuse demyelination of the white matter with sparing of the U fibres, which was explained as being secondary to the interruption of long-fibre systems. The cerebral cortex was involved in both these cases, as indeed it has been in most of the published examples, and the author emphasizes that this disorder is only a peculiar form of cerebral arteriosclerosis and not a distinct disease entity.

Bernard Isaacs

1357. **Brain Disease in Chronic Listeriosis.** (О заболеваниях головного мозга при хронической форме листереллезной инфекции)

A. S. SITOVIC. *Журнал Невропатологии и Психиатрии* [Zh. Nevropat. Psikhiat.] 62, 880-885, No. 6, 1962. 15 refs.

This author reports an investigation of 60 women who were under observation for complications of pregnancy and in all of whom a diagnosis of listeriosis was made, in most cases by a positive serum complement-fixation reaction with *Listeria* antigen in titres ranging from 1:10 to 1:320. In some cases the organism was found in the mother's blood, in the meconium or, when the infant died, in its internal organs. The patients were divided rather arbitrarily into 3 overlapping groups of about equal size. Those in the first group were considered clinically normal. Those in the second group complained of headache, dizziness, nervousness, irritability, frequent weeping, tiredness, insomnia, and muscle and joint pains, and examination revealed emotional lability, sweating, acrocyanosis, generalized tremor, and, in most of the cases, slight pupillary irregularity, slight squint, flattening of one or other naso-labial fold, asymmetry of the tendon jerks, or doubtful plantar responses. The patients in the third group were considered to have clear evidence of organic brain disease; neurological signs were slight, although squint was a frequent finding; the principal mental symptom seems to have been difficulty in thinking. One patient at least would often lose her way. Of these patients' children, 13, ranging in age from one to 3 years, were also investigated; 3 were perfectly healthy; the remainder had abnormalities varying in severity from irritability, nervousness, and poor physique to hydrocephalus, oxycephaly, epilepsy, and dementia. In 4 of these the serum reaction for listeriosis was positive.

G. P. McGovern

1358. **Cerebral Cysticercosis in Poland. Clinical Symptoms and Operative Results in 132 Cases**

L. STEPIEN. *Journal of Neurosurgery* [J. Neurosurg.] 19, 505-513, June, 1962. 32 refs.

Few affections of the nervous system present so diverse a picture as cysticercosis. The signs and symptoms depend on the number of parasites, their location, and their stage of development, as well as on the pathological changes they cause in the brain and the individual susceptibility of the host. The author reports that 1.22% of all admissions to a large neurosurgical centre in Warsaw during an unspecified period proved to have cysticercosis, and in the present paper he describes the clinical features and results of operative treatment in 132 cases.

The cases were classified into 3 groups. Group I consisted of those presenting as cases of intracranial space-occupying lesions—that is, with rising intracranial pressure and focal neurological deficit. Out of 55 such cases, recovery or improvement occurred in 74.5% and the operative mortality was 23.6%. Group II consisted of cases of mul-

multiple cysticercosis producing severe cerebral oedema and symptoms of a diffuse cerebral lesion. This type is commonest in children. Out of 34 such cases, 52.9% were improved by decompression operations. Group III consisted of cases in which the parasites induced chronic obliterative meningitis or ependymitis with the development of hydrocephalus. In these cases the least favourable results were obtained following palliative surgery. Out of 43 patients, only 27.9% improved and 67.4% died. J. V. Crawford

EPILEPSY

1359. Reading Epilepsy

G. M. LASATER. *Archives of Neurology* [Arch. Neurol. (Chic.)] 6, 492-495, June, 1962. 2 figs., 7 refs.

The author describes 3 cases in which reading provoked a major epileptic seizure and a fourth case (in a sister of one of the other patients) in which reading produced involuntary movements of the jaw. This last symptom usually preceded the fit in the other 3 cases. The author could find only 20 such cases in the literature. In all cases fairly prolonged reading was needed to bring on the fit, which was caused by no other stimulus. Anticonvulsants seemed to be of limited value in the treatment of the condition, but the patient could usually prevent the fit by stopping reading when the involuntary jaw movement began. One patient never developed an attack when she read Spanish.

G. S. Crockett

1360. Trimethadione in Serum of Patients with Petit Mal Epilepsy

B. N. JENSEN. *Danish Medical Bulletin* [Dan. med. Bull.] 9, 74-79, June, 1962. 6 figs., 5 refs.

It is pointed out that troxidone (3:5:5-trimethyl-2:4-oxazolidinedione) is given in the treatment of petit mal, but no practical method for its estimation in body fluids has been described. Troxidone is demethylated in the body to 5:5-dimethyl-2:4-oxazolidinedione (DMO), which can be estimated in the plasma or serum by ultraviolet spectrophotometry. In a series of 48 patients with petit-mal epilepsy the author, at the University of Aarhus, Denmark, set out to investigate: (1) DMO levels in the serum after the oral administration of troxidone; (2) the relationship between the dose of troxidone and the serum DMO concentration over a longer period; (3) the elimination of DMO as expressed by the decrease in serum concentration and changes in elimination after the administration of sodium bicarbonate or of acetazolamide; (4) the changes in serum DMO levels in a febrile patient. The technique of serum DMO determination by ultraviolet spectrophotometry is described

1361. The Treatment of Minor Epilepsy in Children with Methylethylsuccinimide. (Erfahrungen bei der Behandlung kleiner epileptischer Anfälle im Kindesalter mit Methyl-Äthyl-Succinimid (MAS))

A. MATTHES and E. MALLMANN-MÜHLBERGER. *Münchener medizinische Wochenschrift* [Münch. med. Wschr.] 104, 1095-1098, June 8, 1962. 1 fig.

Ethosuximide was given at the University Children's Clinic, Heidelberg, to 73 children aged 8 months to 14 years suffering from different types of minor epilepsy. The largest group consisted of 47 patients with pyknolepsy; other groups were 11 patients with myoclonic epilepsy, 8 with "salaam attacks", and 7 with psychomotor epilepsy. In 25 patients one of the above types was combined with grand mal. Of the group with pyknolepsy, 77% were rendered free from seizures and in 13% the reduction in number of seizures exceeded 50%. About half of the patients with myoclonic epilepsy became free from attacks, but those experiencing "salaam attacks" were not improved by the drug. Patients with psychomotor epilepsy responded only when the electroencephalogram showed that the epilepsy was of the centrencephalic type. The average dose of the drug was 0.5 to 1 g. daily, although in some cases 2 g. was needed. In three-quarters of the cases benefit was apparent within 14 days.

Side-effects, which were slight, consisted mainly in gastric disturbances; no serious toxic effects were encountered. Grand-mal attacks appeared to be released in 4 patients who had not previously had such attacks. The authors conclude that ethosuximide is at present the drug of choice in pyknolepsy, but that it may also be useful in myoclonic epilepsy, in which case it should be combined with an anticonvulsant drug designed to prevent grand mal. For "salaam attacks" corticotrophin and corticosteroids remain the drugs of choice. J. B. Stanton

1362. Ethosuximide in the Treatment of Epilepsy

S. LIVINGSTON, L. PAULI, and A. NAJMABADI. *Journal of the American Medical Association* [J. Amer. med. Ass.] 180, 822-825, June 9, 1962. 2 figs., 20 refs.

The use of the succinimides (phensuximide, methsuximide, and ethosuximide) in the treatment of epilepsy is discussed. Improvement was observed in 17 of 21 of our patients with petit mal epilepsy who were treated with ethosuximide: complete control was obtained in 8 and partial control in 9 patients. All of these 21 patients had been treated previously with trimethadione without benefit. No significant untoward reactions were observed in any of our 21 patients treated with ethosuximide.

Plans for further investigation of the effectiveness and toxicity of ethosuximide are briefly discussed.—[Authors]

Psychiatry

1364. Electro-encephalographic Observations in Psychotic Children

D. GOLDMAN and B. ROSENBERG. *Comprehensive Psychiatry* [Comprehens. Psychiat.] 3, 93-112, April [received June], 1962. 7 figs., 10 refs.

The application of electroencephalography (EEG) in child psychiatry has been neglected, yet the few reported investigations establish a high correlation between abnormalities in the EEG and abnormal behaviour and psychological functioning.

The present authors describe the EEG findings in 134 severely disturbed children admitted to Longview State Hospital, Cincinnati, Ohio, over a period of one to 10 years, these representing practically all the admissions to the children's unit, which was established in 1950 [criteria for selection are not given]. There were 90 boys and 44 girls aged 6 to 13 years, 83 of the children being between 11 and 13 years. The EEG findings were correlated with the diagnoses made by the hospital staff from clinical and laboratory studies, excluding EEG.

The EEG was "normal" in only 16 (12%) of the patients. Of 35 children in whom chronic brain syndrome was diagnosed (organic, post-traumatic, and convulsive disorders) the abnormalities were focal in 5, convulsive in 28, and borderline in 2. In 31 children in whom schizophrenia was diagnosed the corresponding figures were 0, 8, and 18 (5 children in this group had a normal EEG); in 52 children with personality disorders the figures were 2, 27, and 14 (9 in this group had a normal EEG).

Compared with other diagnostic groups schizophrenics showed a greater degree and frequency of abnormality under thiopentone activation. The EEGs in 2 cases, which are reproduced, show that there is a reduction in this thiopentone activity when phenothiazine derivatives result in clinical improvement, but not otherwise.

The authors emphasize the frequency of abnormal EEGs in what appeared to be "function" behaviour disorders and psychoses. They suggest that the earlier in life such illness is manifest, the more likely is it that there will be underlying organic brain disorder. They correlate maturation of electrical activity of the brain with improved integration of behavioural and mental functioning. *Christopher Wardle*

1365. Old Folk in Wet Beds

J. L. NEWMAN. *British Medical Journal* [Brit. med. J.] 1, 1824-1827, June 30, 1962. 4 refs.

The author of this paper from Green Lane Hospital, Auckland, New Zealand, suggests that much of the incontinence (so-called) in the aged is artificially produced by such factors as unnecessary immobility, delay with bottles and bed-pans, and administration of hypnotics without allowing for micturition during the night. He considers that insufficient allowance is made for unaccustomed posture. In short, he questions the currently accepted views on the causes of urinary incontinence, especially the view that senile dementia is the most important factor.

The causes of true incontinence are: (1) neurogenic (sensory and motor); (2) traumatic (vesico-vaginal fistula);

(3) bladder-neck disturbances; and (4) dementia, when profound. Not satisfied that these comprise all the causes of incontinence, the author seeks another and finds it in Pavlov's concept of psychological breakdown under stress—the stress being the artificial and restricted environment which the average geriatric ward imposes on patients who have previously been free or relatively free to attempt to fend for themselves.

[This is, perhaps, a too brief summary, but the full value of this excellent paper, with its unusually frank observations, can be appreciated only by reading it in its entirety.]

Rex Matthews

1366. Investigation of the Palmar Sweat Count of Young Male Subjects under Normal Conditions

P. C. B. MACKINNON, A. H. GOULD, and J. HARRISON. *Psychosomatic Medicine* [Psychosom. Med.] 24, 234-239, May-June, 1962. 3 figs., 14 refs.

A study of palmar sweat-gland activity in healthy subjects is described in this paper from the Royal Free Hospital School of Medicine and the Army Occupational Research Group, London. Over a 7- to 28-day period a daily count was made in 20 male students (aged 18 to 31 years) of the number of active sweat glands in a standard area 4 mm. square of the pad of the right middle finger. The technique used was that of Sutarman and Thomson (*J. Physiol.*, 1952, 117, 51).

The study revealed the existence of two basically different groups of subjects: (1) a "regular" group (6 subjects) with a low daily variance of sweat-gland activity, and (2) an "irregular" group (14 subjects) manifesting a high daily variance. To test the validity of this finding a second investigation was carried out in 6 "regular" subjects and in 6 from the "irregular" group selected at random. In spite of a statistical anomaly in the choice of one subject in the "irregular" group, the results of the second investigation lent support to the hypothesis that two distinct groups existed. Not only did basic levels of palmar sweating vary significantly between individuals, but also each individual displayed unpredictable alterations over a period of time. It is suggested that the individual and group differences are probably determined by both physiological and emotional factors.

A. Balfour Sclaire

1367. Purpura as a Psychosomatic Entity: a Psychiatric Study of Autoerythrocyte Sensitization

D. P. AGLE and O. D. RATNOFF. *Archives of Internal Medicine* [Arch. intern. Med.] 109, 685-694, June, 1962. 27 refs.

A clinical study of autoerythrocyte sensitization is reported in this paper from Western Reserve University School of Medicine and University Hospitals of Cleveland, Ohio. This syndrome, which is characterized by a chronic purpuric state, was first described by Gardner and Diamond (*Blood*, 1955, 10, 675; *Abstr. Wild Med.*, 1956, 19, 53).

The haematological examination and psychiatric features in a group of 9 female patients aged 19 to 51 years were studied. Six of the patients were interviewed directly and

3 were studied retrospectively from a review of the case records. The most frequent symptoms were ecchymosis, menorrhagia, epistaxis, and alimentary haemorrhage. No haemostatic defect was discovered, but in each case ecchymosis was produced after intracutaneous injection of the patient's own blood. In 3 patients bruising was also produced by the intracutaneous injection of saline. All 9 patients manifested a marked tendency towards conversion hysterical reactions and 8 of them had severe interpersonal problems. Hysterectomy had been carried out in 4. Of the 6 patients directly interviewed 5 gave evidence of acute emotional stress immediately before the episodes of purpura.

It is not known whether the purpuric attacks and autoerythrocyte sensitization were the symbolic expression of emotional conflicts or were the result of lowered capillary threshold to peripheral stimuli owing to emotional stress. The authors suggest that it would be worth exploring the possibility of psychiatric treatment in such cases.

[No details of haematological investigations are given.]

A. Balfour Sclaire

1368. Influence of Family Life on the Course of Schizophrenic Illness

G. W. BROWN, E. M. MONCK, G. M. CARSTAIRS, and J. K. WING. *British Journal of Preventive and Social Medicine* [Brit. J. prev. soc. Med.] 16, 55-68, April [received June], 1962. 14 refs.

The domineering, over-solicitous behaviour frequently found in the mothers of schizophrenic patients may be a result or a cause of the abnormality in the children. This paper from the Maudsley Hospital, London, follows an earlier study in which it was suggested that family relationships can influence the course of schizophrenia.

A total of 128 schizophrenic men aged 20 to 49 years were observed for one year, after discharge from hospital; 72 deteriorated and 53 of these were readmitted. The following rating scales were used: (1) clinical condition at discharge, based on rating of mental state during an interview with a psychiatrist and the nurse's report of socially embarrassing behaviour in the ward during the previous week; (2) emotional involvement exhibited between the patient and the relative to whom he was discharged, based on a rating of the degree of emotion and hostility expressed by each to the other and the degree of dominant or directive behaviour shown by the relative to the patient; (3) deterioration of behaviour during the year of observation, rated on the same criteria as the first scale; (4) "time budget" of the patient's social activities; this measured the amount of face-to-face contact between patient and relative.

Deterioration occurred in a higher proportion of patients rated more disturbed on discharge. It was commoner in patients who were under 20 at the time of first admission, who had been in hospital for more than 6 months, and who before admission showed signs of disruption of social and occupational adjustment (unemployment, decline in occupational level, disturbed behaviour). The higher the rating of emotion and hostility expressed by the relative, the more frequently did the patients deteriorate. Rating of dominance by a relative showed a similar but not significant relationship. Patients rated high in hostility to their relative deteriorated significantly more frequently. Of patients returning to a home rated high in emotional involvement, 76% deteriorated, in contrast to 28% returning to a home rated low in emotional involvement. This was found to be

independent of the patient's mental state on discharge. The hypothesis that the less contact patients in highly emotional homes had with relatives the less likely would they be to deteriorate was confirmed only for the patients who were more disturbed on discharge. The proportion of patients who deteriorated was similar for those discharged to relatives and those discharged to lodgings. This contrasts with the authors' previous finding of a lower proportion deteriorating in lodgings. The special features of social isolation which may be beneficial to the discharged schizophrenic patient are discussed.

Christopher Wardle

AFFECTIVE DISORDERS

1369. An Evaluation of Tranlycypromine ("Parnate") in the Treatment of Depression

A. A. BARTHOLOMEW. *Medical Journal of Australia* [Med. J. Aust.] 1, 655-662, May 5, 1962. 2 figs., 40 refs.

A double-blind sequential trial of tranlycypromine in the treatment of depressive illness is reported. Tranlycypromine, which is a monoamine oxidase inhibitor, is claimed to be of value in this type of illness.

The patients were selected from a consecutive series seen and treated at the Alexandra Clinic, Department of Mental Hygiene, Victoria, Australia. They were matched in pairs for age and sex and for severity and duration of the depressive state and were given tranlycypromine in a dosage of 30 mg. daily, increased to 60 mg. daily if this was thought necessary. Treatment was given for 6 weeks and the patient's condition then assessed clinically as "markedly improved", "moderately improved", or "not improved". Compared with a placebo, tranlycypromine was found to be of value in the treatment of depressive illness, but this was so only in patients with "reactive depression"; no significant difference was seen in patients with endogenous or involutional depression. Improvement, when it occurred, began within 2 weeks of starting treatment. Side-effects, which were few, included hypomania, dependent oedema, impotence, and nausea and vomiting.

It is concluded that tranlycypromine is of value in the milder types of depressive illness.

B. M. Davies

1370. Short-term and Long-term Treatment of Depression with Laroxyl (Amitriptyline). (Kurz- und Langzeitbehandlung der depressiven Syndrome mit "Laroxyl" (Amitriptylin))

F. JOST and E. WEBER. *Praxis* [Praxis] 51, 650-656, June 21, 1962. 5 figs., 18 refs.

At the Beverin in Casis Hospital, Graubünden, Switzerland, 62 depressive patients were treated with amitriptyline ("laroxyl"), at first as in-patients and later as out-patients. The group included 32 patients with endogenous depression, 14 with psychogenic depression, 9 depressive schizophrenics, and 7 suffering from depressive states with an organic background. The average daily dosage of amitriptyline was 150 to 200 mg. Clinical recovery or great improvement was achieved in 46 patients, while 16 failed to respond. Side-effects, consisting chiefly of vegetative disturbances such as dryness of the mouth and constipation, appeared in about one-third of the patients. The average stay in hospital was 28.6 days and the total duration of treatment was 6 to 12 months. The authors warn that in patients who have previ-

ously been treated with monoamine oxidase inhibitors, amitriptyline must be used with caution. One of their patients attempted suicide by taking 1,000 mg. of the drug, but recovered.

J. B. Stanton

1371. **Ambulatory Treatment of Depressive States with "Laroxyl".** (Die ambulante Behandlung depressiver Zustände mit Laroxyl (Roche))
V. E. GSCHLACHT. *Praxis [Praxis]* 51, 657-660, June 21, 1962. 2 figs., 11 refs.

The author discusses the effects of amitriptyline ("laroxyl"), which he regards as a genuine thymoleptic. Its action begins with an initial phase of sedation, relaxation, and reduction of anxiety, and passes into a main phase of relief of depression and increase in drive. The author treated 35 out-patients with depressive syndromes with initial doses of 30 mg. of amitriptyline daily, and increased the dosage after a week to 75 mg. or even 150 mg. daily. When symptoms of depression had subsided a daily maintenance dosage of 10 to 20 mg. was given for several months to prevent relapse. The best results were obtained in involuntal depression, all 8 patients with this condition being cured and able to dispense with maintenance therapy. In 30 of the patients the response to amitriptyline was favourable, and in 22 the symptoms disappeared completely. The sedative action of amitriptyline makes it particularly useful in cases of agitated depression, and with the above dosage the author found practically no side-effects. The anti-depressive effect of amitriptyline was as good as that of imipramine, appearing sooner after the beginning of treatment, and stronger than that of chlorprothixene ("taractan").

J. B. Stanton

1372. **First Results with a New Antidepressant Drug, "Laroxyl".** (Premiers résultats obtenus avec un nouveau médicament antidépresseur: le laroxyl)
G. LAI. *Psychiatria et neurologia [Psychiat. et Neurol. (Basel)]* 143, 352-363, 1962. 1 fig., 6 refs.

In trials of amitriptyline ("laroxyl"), a derivative of dibenzocycloheptadiene structurally related to imipramine, in 40 depressive patients at the University Psychiatric Clinic, Lausanne, the best results were obtained in endogenous depression and neurotic depression with anxiety. Amitriptyline differed from imipramine in producing less benefit in senile and organic depressions. In addition to its effect on mood and anxiety, it had a marked sedative action which was beneficial in neurotic depression. It produced fewer side-effects than imipramine, particularly in the circulatory system, but in some cases, chiefly older patients, it precipitated confusional states.

J. B. Stanton

1373. **Treatment of Depression with a New Antidepressant, "Laroxyl".** (Depressionsbehandlung mit einem neuen Antidepressivum "Laroxyl" (Roche))
R. THALMANN. *Praxis [Praxis]* 51, 671-676, June 28, 1962. 9 refs.

The above is a report on the treatment of depression with a new antidepressive, "laroxyl", based on studies of 68 hospitalized patients. The period of study extended up to six months. In the majority of cases the treatment was at first administered parenterally and after the onset of action orally. The dosage in no case exceeded 200 mg. a day, a gradual reduction to a maintenance dose of 50 to 100 mg.

taking place as the effect became apparent. The laboratory findings (blood counts, liver function tests) yielded no significant changes. There was no appreciable change in the blood pressure and pulse arising from the preparation. Onset of action was observed at the latest after the first week. Mention is made of the side effects, notably dryness of the oral mucosa, in some cases slight vertigo and sleepiness, especially at the beginning of the treatment, and a slight tremor of the fingers. Laroxyl definitely has the effect of dispelling depression and can be classed as a thymoleptic. The indications are the same as for "tofranil". Even although numerically the purely depressive psychoses reacted best to laroxyl, a certain neuroleptic component can be assumed from the improvements observed in the case of depressive schizophrenia.—[Author's summary.]

1374. **A New Antidepressant, Amitriptyline ("Tryptizol"); Clinical Trials.** (Un nouveau psycholeptique, l'amitriptyline (tryptizol); expériences cliniques)
G. ABRAHAM and D. PANAYOTOPOULOS. *Praxis [Praxis]* 51, 677-680, June 28, 1962. 8 refs.

The authors, at the Malévoz Mental Hospital, Monthey, Switzerland, used amitriptyline ("tryptizol") in the treatment of 83 in-patients and 13 out-patients with various forms of depression, including 28 cases of schizophrenia with depressive features. Very good results were reported in 20 cases, satisfactory results in 39, doubtful improvement in 26, and no effect in 11. The results were best in endogenous depression and involuntal melancholia; in manic-depressive psychosis (in the depressive phase) and in reactive depression they were less predictable. The drug was found useful in the disturbed stage of alcoholism when depression was prominent and in the more acute schizophrenic depressions. Side-effects were few, and the tendency for swing to hypomania sometimes seen during the administration of imipramine was not observed with amitriptyline. Relapses did not occur during the period of follow-up before publication of this paper, although in 3 cases premature withdrawal of the drug caused recrudescence of symptoms. The authors conclude that amitriptyline is a drug of therapeutic value.

J. B. Stanton

1375. **Clinical Trial with Desmethylinipramine (G-35020), a New Antidepressive Compound**
T. A. BAN and H. E. LEHMANN. *Canadian Medical Association Journal [Canad. med. Ass. J.]* 86, 1030-1031, June 2, 1962. 8 refs.

Research work has suggested that the antidepressant action of imipramine ("tofranil") depends on an active metabolite, and this was isolated by Brodie and his colleagues as desmethylinipramine (DMI). The present paper describes a trial of DMI in the treatment of 25 patients with depressive illness at the Protestant Hospital, Verdun, Quebec. The patients were usually given 75 mg. of the drug per day for a week, and thereafter 150 mg. per day, treatment being continued for 10 weeks. As assessed on clinical grounds, 74% of the patients were regarded as "recovered or much improved". Side-effects occurred in about one-third of the patients; these included insomnia, hypomania (in 2 cases), dryness of mouth, sweating, and mydriasis. Extrapyramidal symptoms occurred in one patient.

The authors consider that desmethylinipramine may be more active and produce fewer side-effects than the parent

compound. [Despite the absence of controls, this study is of interest in view of similar studies with imipramine.]

B. M. Davies

TREATMENT

1376. The Present Indications for Leucotomy

W. SARGANT. *Lancet* [*Lancet*] 1, 1197-1200, June 9, 1962.

The author shows from his own very considerable experience that leucotomy still has a valuable part to play in helping selected patients who have failed to respond to all other treatments. A variety of modified leucotomy techniques can now replace the full operation, especially when used in conjunction with tranquillizing and antidepressant drugs. The operation should be confined to a thorough section of the lower medial quadrants of the frontal lobes only, and if misplaced cuts and large haemorrhages are avoided maximum benefit can be obtained with minimum deleterious effects. Youth is often a bar to success and patients tend to do much better when they are middle-aged or even elderly. The possibility of re-operation must be kept in mind when a patient has done well for some weeks and then has a relapse.

In the past 20 years at St. Thomas's Hospital, London, and Belmont Hospital, Sutton, Surrey, leucotomy has usually been reserved for chronic neuroses or depressive states. The author states that with careful selection good results can be obtained in 80% or more of such patients. None of these patients were operated upon without long periods of previous treatment and very careful study, usually in hospital. The advantages of psychiatric beds in general hospitals is stressed; patients such as neurotics are rarely willing to stay long in mental hospitals. The author also points out that the patient's pre-illness personality often proves the main deciding factor in the final outcome.

Discussing the controversial problem of leucotomy in schizophrenia the author states that after a "full and thorough section of the lower medial quadrants, done a little farther back than in the neuroses", followed by administration of tranquillizing drugs, a worthwhile proportion of patients were able to return home.

It is concluded that with the discovery of more specific drugs for the relief of schizophrenia and neuroses with strong obsessive components the need for leucotomy will diminish. Till then, however, it will have its place as one of the methods of treatment of certain forms of intractable mental illness.

J. V. Crawford

1377. A Five-year and Ten-year Follow-up Study of Patients Treated with Sub-coma Insulin

H. GRAUER and G. J. SARWER-FONER. *Medical Services Journal, Canada* [*Med. Serv. J. Can.*] 18, 371-382, May, 1962. 17 refs.

At Queen Mary Veterans Hospital, Montreal, two groups of patients were followed up 5 and 10 years respectively after psychotherapy and administration of subcoma doses of insulin, no other specific therapy having been given. In all cases 20 to 30 treatments were given "with an increasing average dose" of insulin up to 60 units in the 10-year group and 110 units in the 5-year group. The conditions diagnosed were anxiety and depressive states, personality disorders, and "borderline states" [*sic*]. There were no statistically significant differences between the two groups in degree of insight shown, reaction to the doctor, subjective

reactions to insulin treatment, or the degree of success obtained as judged by the patients themselves and from their employment records and records of readmission to hospital. Only 10% had been readmitted for psychiatric reasons. The authors consider the therapeutic results "relatively good", but there was no basic change in the personality structure of the patients. The treatment appeared to have supported them over isolated periods of stress. Of the 10-year group 74% were working and well integrated into the community.

Under one-third of the original patients in the 10-year group and less than one-half of the 5-year group were traced and interviewed.

J. N. Agate

1378. The Modifications of a Side Effect (Drowsiness) of Chlordiazepoxide ("Librium") by Amiphenazole

A. A. BARTHOLOMEW and D. W. BRUCE. *Medical Journal of Australia* [*Med. J. Aust.*] 1, 927-928, June 16, 1962. 7 refs.

Since patients taking chlordiazepoxide often complain of drowsiness the authors set out to determine whether this drowsiness could be reduced by giving the drug together with amiphenazole. A group of 36 patients (including 15 "remitted alcoholics", 11 "mixed neurotics", and 10 patients with character disorders) were given identical-appearing tablets containing 20 mg. of chlordiazepoxide, or 200 mg. of amiphenazole, or both drugs together, the tablets being taken 3 times daily for 6 weeks. Patients were asked about the general effect of the tablets, but no specific inquiry was made concerning drowsiness, the incidence of this being assessed from the comments volunteered by the patients.

Altogether 12 patients experienced drowsiness, 3 receiving the combined treatment, 2 receiving amiphenazole, and 7 chlordiazepoxide; in 2 patients in the last group drowsiness was "very marked". By a chi-square test the probability of such a result is more than 0.05; however, the authors consider that this need not be taken "too seriously", since the design of the trial was not statistically rigorous and the results were "clinically unequivocal". Further clinical confirmation of the observed antagonism is necessary.

Alan A. Black

1379. An Unfortunate Effect from the Ill-judged Self-administration of Chlordiazepoxide ("Librium")

C. H. NOACK. *Medical Journal of Australia* [*Med. J. Aust.*] 1, 930-931, June 16, 1962. 13 refs.

The author's experience of chlordiazepoxide in the treatment of 100 patients at the Observatory Clinic, Melbourne, confirms most other reports that drowsiness is the principal side-effect of the drug. Dizziness with or without ataxia has only rarely been noted.

An exceptional case is described, that of a 37-year-old man suffering from a severe anxiety state who momentarily lost consciousness on the second day of taking chlordiazepoxide in a fixed routine dosage. This occurred while the patient was driving slowly in rush-hour traffic; the resulting minor collision immediately awakened him, and although he was not otherwise affected, he was afraid to take the drug again. Subsequently the symptoms were satisfactorily controlled by restricting the drug to periods of maximum tension only.

Variation in personal tolerance and the need to adjust the dosage to suit individual requirements are emphasized.

Alan A. Black

Dermatology

1380. Dermatitis Caused by Formaldehyde Resins in Textiles. [In English]

P. V. MARCUSSEN. *Dermatologica* [*Dermatologica* (Basel)] 125, 101-111, 1962. 4 figs., 13 refs.

Certain anhidrotic agents contain formaldehyde, while formaldehyde resins are widely used in the preparation of crease-resisting and "non-iron" textiles. The present author quotes from the literature and from his own experience at the Finsen Institute, Copenhagen, to demonstrate that the number of patients with formaldehyde dermatitis from textiles has increased markedly during the last 10 years, and states that during the same period the number of patients with formaldehyde dermatitis from anhidrotics has decreased. In 35 of 96 patients with reproducible positive reactions to patch tests with 4% aqueous formaldehyde investigated during 1959 and 1960 the sensitization was associated with clothing. The sides and back of the neck were the areas most commonly affected. The author describes a simple chemical test for detecting formaldehyde in clothing samples. This test has proved of value in identifying the offending textiles in the patients' wardrobes and in assisting them to buy new articles of clothing. Patients with formaldehyde hypersensitivity show a tuberculin-type reaction to formaldehyde injected intradermally; this test is, however, impracticable since normal subjects also develop necrosis of the skin with formaldehyde at a slightly higher concentration. There is no simple explanation for the comparative rarity of formaldehyde dermatitis in spite of the facts that there is almost universal exposure through textiles and that the chemical is a potent skin-sensitizing agent. Only a small number of subjects with formaldehyde hypersensitivity develop dermatitis when exposed to textiles containing formaldehyde.

P. T. Main

1381. Abnormalities of the Finger Nails Associated with Impaired Peripheral Blood Supply

P. D. SAMMAN and B. STRICKLAND. *British Journal of Dermatology* [*Brit. J. Derm.*] 74, 165-173, May, 1962. 5 figs., 11 refs.

The nail changes in 41 patients with symptoms suggestive of peripheral vascular disease are described in this paper from the Westminster and St. John's Hospitals, London. The most characteristic change is one which affects many nails and is associated with symptoms of arterial spasm, often of many years' duration. The nails are thin, brittle, and excessively ridged in a longitudinal direction. They tend to split at the free edge along the ridges, and because of this brittleness the nails are usually rather short. The surface of the nail plate is irregular and there is variation in colour. Separation of the nail from its bed may occur. Uncommonly, yellow or greenish nails are seen (4 patients in this series); these nails appear to stop growing. The colour is not due to infection with *Candida* or *Pseudomonas pyocyanea*. Complete shedding of one or more nails, which was observed occasionally, may take place independently of local gangrene. Permanent loss with scarring may be seen. In 3 patients flaking of the surface and partial loss of

the nails occurred. Subclavian arteriography was carried out in 13 patients and in the majority of these there was considerable abnormality of the digital vessels.

S. T. Anning

1382. Benign Disseminated Reticuloendotheliosis of the Skin in Infancy. (Die benigne disseminierte Reticuloendotheliose der Haut im Kleinkindesalter)

R. ILLIG and G. FANCONI. *Annales paediatrici* [*Ann. paedlat.* (Basel)] 199, 47-73, 1962. 15 figs., 24 refs.

The terms reticuloendotheliosis and histiocytosis X are currently used to include the syndromes of Hand-Schüller-Christian, Letterer-Siwe-Abt, and Lichtenstein-Jaffe (eosinophilic granuloma), which are thus distinguished from the reticuloses. Although each of these syndromes affects a distinctive group of organs, their basic pathology is the same, namely, an abnormality of the histiocytes or reticuloendothelial cells and of the eosinophil granulocytes, followed by secondary deposition of cholesterol and lipids. The unitary interpretation is supported by the frequency of transition from one syndrome to another, the occurrence of mixed forms, and the identification of pathology of each type in the same patient. The authors, writing from the University of Zürich, here describe a new subgroup based on 4 patients, in whom the presenting features were identical with those of histiocytosis X, but who recovered completely. The syndrome appeared before the age of 3 years, and all the patients had maculo-papular, and occasionally granulomatous, reddish-brown skin lesions on the trunk and head. The authors relate their 4 cases to 9 similar cases reported in the literature in which lesions of the skin and mucous membranes, otitis, and a form of eosinophilic granuloma of bone were the chief features. The bone marrow, spleen, liver, and lymph nodes were not affected. Histological examination showed reticular-cell involvement in all cases. Treatment with corticosteroid drugs administered systemically and local irradiation aborted the disease in the authors' patients, and complete cure is recorded in all the cases reported. The authors consider that these 13 cases constitute a subgroup and propose the name "benign disseminated reticuloendotheliosis of the skin in infants".

Allene Scott

1383. Treatment of the Whole Body Surface with Electrons. L. SZUR, J. A. SILVESTER, and D. K. BEWLEY. *Lancet* [*Lancet*] 1, 1373-1377, June 10, 1962. 7 figs., 8 refs.

At St. John's Hospital for Diseases of the Skin or at Hammersmith Hospital, London, 9 patients with widespread skin disease were treated with electron therapy. Five had mycosis fungoides, 2 exfoliative dermatitis, one generalized psoriasis, and one erythroderma. A Medical Research Council 8-MeV. linear accelerator was used to give a wide electron beam, but a carbon decelerator of varying thickness was added which determined the penetration suitable to the individual patient while at the same time giving a still wider electron scatter. For the cases of exfoliative dermatitis and the less severe cases of mycosis a 2-cm. carbon decelerator was used, giving an 80% depth

dose at 4.5 mm., whereas for the more severe cases of mycosis a 1.75-cm. carbon decelerator was used, giving an 80% depth dose at 6.5 mm.

In all except one case rapid improvement was obtained, but although the follow-up period has been short it appears that recissions are likely. Repeat treatment has been successfully given to one patient. Examination of the peripheral blood during and after treatment did not show any evidence of bone-marrow depression in the majority of patients, but in a few cases there was some reduction in the number of circulating lymphocytes and platelets, although this was not severe enough to necessitate the interruption of treatment. *E. H. Johnson*

1384. Triamcinolone Acetonide in Cutaneous Lesions

A. A. EISENBERG and J. M. RIDDELL JR. *Texas State Journal of Medicine [Tex. St. J. Med.]* 58, 407-410, June, 1962. 5 refs.

The authors report good results from the local injection of triamcinolone acetonide into lesions of lichen, eczema, psoriasis, and keloid. The injections may be painful and local atrophy sometimes follows. [The period of observation in the 40 cases is not mentioned.] *John T. Ingram*

1385. Triamcinolone Acetonide Spray; Its Use in Chronic Dermatoses

S. M. FORD. *Texas State Journal of Medicine [Tex. St. J. Med.]* 58, 411-414, June, 1962. 2 figs., 3 refs.

Triamcinolone acetonide spray was used in the Department of Dermatology, Baylor University College of Medicine, Houston, Texas, in the treatment of 117 patients with chronic eczema, psoriasis, and lupus erythematosus, the period of observation varying from 2 to 10 months. Moderately good results were obtained in lupus erythematosus and in psoriasis of the scalp and flexures, and most patients with eczema responded well. The spray was regarded as being more effective than creams, though frequent spraying of normal skin was liable to provoke blackhead formation. *John T. Ingram*

1386. Management of Infantile Eczema

J. T. INGRAM. *British Medical Journal [Brit. med. J.]* 2, 44-46, July 7, 1962. 8 refs.

Infantile eczema is a result of exceptional skin sensitivity that is often a part of general sensitiveness or awareness. The provocative cause of a particular attack may be extremely trivial, but heightened susceptibility to recurrence lasts long after the clinical attack has cleared. The desire to scratch may give rise to important emotional complications and there is a danger of making the prevention of scratching and the treatment of the rash a ritual that does harm to both child and mother.

Measures for relief are described in this paper. An anti-histamine drug taken internally is valuable because it relieves itching and is tranquillizing, but not because of any anti-histamine property. Hydrocortisone, 1% in a silicone barrier cream, is particularly valuable in local treatment for the head and neck and for the flexures. A cream containing liquor picis carbonis is recommended for the body. Occlusive bandages are of great value because they prevent scratching and because they remove the danger of frequent ritual dressings. Cotton bandages impregnated with hydrocortisone in silicone barrier cream, which can be left in

place for weeks on end, have been found particularly useful for this purpose. There should be no friction to the skin, but baths, not too hot, can often be allowed, with the addition of a little emulsifying ointment. The child must feel secure, but must not be too sheltered from life, as he is usually an individualist. In short, treatment should include mother as well as child. *E. H. Johnson*

1387. Psoriasis: a Disorder of Necrosis

K. C. DIXON, G. A. GRESHAM, and C. H. WHITTLE. *British Journal of Dermatology [Brit. J. Derm.]* 74, 283-287, Aug.-Sept., 1962. 8 figs., 12 refs.

The authors of this paper from the University of Cambridge regard psoriasis as a disorder of necrosis. Specimens for biopsy were taken before treatment from 2 male patients, aged 19 and 80 years respectively, suffering from psoriasis, and from a third male aged 37 years, also with psoriasis, who had already received topical applications of vitamin A and triamcinolone. The oxidized tannin-azo (OTA) method was applied to sections of each tissue and sections were also stained by the Feulgen method and with Harris's haematoxylin and eosin. It was found that tannophilic protein detectable by the OTA method persisted around many of the nuclei in the psoriatic horny layer and that deoxyribonucleic acid (DNA) stainable by the Feulgen method was present in abundance in the persistent nuclei of the psoriatic scales. The DNA was found to be concentrated in the nuclear membranes and in well-defined granules of chromatin.

It is suggested that the persistent synthetic activity of the psoriatic epidermis, including the continued elaboration of tannophilic protein, is governed by the retention of functional DNA in the lamellated nuclei. *R. R. Willcox*

1388. Diffuse Scleroderma and Raynaud's Disease

S. JABLONSKA, B. BUBNOW, and A. SZCZEPAŃSKI. *British Journal of Dermatology [Brit. J. Derm.]* 74, 174-182, May, 1962. 29 refs.

The authors, writing from Warsaw Medical School, Poland, set out to show that in the condition they term "diffuse scleroderma" or "acroscleroderma" with coexistent Raynaud's phenomenon the prognosis is neither as favourable as maintained by some workers nor as grave as claimed by others. [The condition referred to is now usually known in Britain as diffuse sclerosis.]

Of a series of 33 patients, the condition was described as severe in 17 and mild in 16. In 9 of those with the severe type the age at onset was over 40 years. The interval between the onset of Raynaud's phenomenon and the development of skin changes showed some prognostic significance. When the interval was more than 10 years (12 female patients) the course of the illness tended to be slow and extended over many years. In the 5 patients (females) in whom Raynaud's phenomenon preceded "scleroderma" by more than 5 years, but less than 10, the condition was worse. The oesophagus and heart or the oesophagus, heart, and lungs were affected in 4 patients in the latter group.

The authors discuss the value of capillaroscopy and the significance of sensory chronaxy. They state that the prognosis may be grave owing to very frequent visceral involvement (in 27 of the 33 patients). [This does not support their opening observations concerning prognosis.] *S. T. Armitag*

Paediatrics

1389. Infection with *Pseudomonas aeruginosa* in Premature Newborn Infants. (L'infezione da *Pseudomonas aeruginosa* nel neonato immaturo)

F. RAGAZZINI and C. PANERO. *Rivista di clinica pediatrica* [Riv. Clin. pediat.] 69, 73-107, Feb. [received July], 1962. 6 figs., bibliography.

Its high resistance to antibiotics has increased the importance of *Pseudomonas aeruginosa* (*pyocyanea*) as a pathogen. The authors discuss recent papers on infection with *Ps. pyocyanea* in the newborn and describe 35 cases admitted to the Premature Unit of the University Paediatric Clinic at Florence over a period of 18 months. The 28 infants who recovered had symptoms and signs referable to several systems, but one system was predominantly affected—the respiratory tract in 18, the intestines in 5, and the meninges in one, while 4 had localized infections. In the 7 who died necropsy showed widespread infection. It is often difficult to be certain that *Ps. pyocyanea* is the cause of this illness, since other pathogens may also be present.

The authors divided the infants in their series into 3 groups. The first group consisted of those with an undoubted *Ps. pyocyanea* infection, proved bacteriologically.

In the second group, which they regarded as almost certainly cases of *Ps. pyocyanea* infection, the symptoms were predominantly respiratory with, in addition, the common signs and symptoms of a mild but persistent toxæmia, abdominal distension, resistance to antibiotics, and slow resolution of the radiological abnormalities, and *Ps. pyocyanea* was isolated from the nasopharynx. The third group were presumed to be infected with *Ps. pyocyanea*, but there was no laboratory confirmation. The clinical picture was, however, similar to that of the other patients, with equally slow improvement, and they were infected during the same period. Treatment was chiefly with γ -globulin, blood transfusions, and the antibiotics colimycin and polymyxin.

J. G. Jamieson

CLINICAL PAEDIATRICS

1390. Various Childhood Tumors: Treatment with Actinomycin D and X-ray Therapy

E. J. LIEBNER, G. P. KIRKPATRICK, and I. M. ROSENTHAL. *Illinois Medical Journal* [Illinois med. J.] 121, 531-537, May, 1962. 9 figs., 26 refs.

Actinomycin D has been reported to have a favourable effect on certain tumours, particularly Wilms's tumour and rhabdomyosarcoma. The present authors, at the University of Illinois Research and Education Hospitals, Chicago, treated 11 cases of neoplasm in children with the drug; each patient receiving intravenously doses varying from 0.2 to 0.4 mg. daily for 5 days. Most patients had 2 courses, but 2 patients had 3 and 4 courses respectively. An attempt was made to give x-ray therapy 4 hours after administering the drug, but this was not always feasible. Four children, 3 with Wilms's tumour and one with a laryngeal rhabdomyosarcoma, greatly benefited from the treatment; but no improvement was noted in cases of neuroblastoma or of Wilms's

tumour with metastases. There was temporary improvement in a child with Hodgkin's disease and another with Ewing's sarcoma. Toxic effects were severe and numerous, and included dermatitis, stomatitis, thrombophlebitis, leucopenia, and anaemia.

The authors consider that the favourable results already obtained justify a more aggressive approach to the treatment of malignant disease in childhood, with the use of the newer antibiotic and chemotherapeutic agents in combination with radiotherapy.

J. G. Jamieson

1391. The Character of the Microflora and Its Antibiotic Sensitivity in the Treatment of Acute Non-specific Lymphadenitis in Children. (Характер микрофлоры и ее чувствительность к антибиотикам при лечении острых неспецифических лимфаденитов у детей)

JU. A. AKIMOV. *Voprosy Okhraṇy Materinstva i Detsstva* [Vop. Okhran. Materin. Dets.] 7, 52-55, June, 1962. 8 refs.

The author remarks that, although acute non-specific lymphadenitis is one of the commonest infections of childhood, it does not always receive the attention it deserves. Because of increased bacterial resistance, antibiotics, whether administered orally or parenterally, no longer produce a prompt and satisfactory result as they did when first introduced. Of 117 children with acute non-specific lymphadenitis investigated, staphylococci were grown from the lesions in 94, streptococci in 5, and diplococci in 3; in 15 the lesions were sterile. The staphylococci isolated were *Staphylococcus albus* in 62 (haemolytic in 21, non-haemolytic in 27, and weakly haemolytic in 14) and *Staph. aureus* in 32 (haemolytic in 13 and non-haemolytic in 19). In only 14 of the children did the condition respond to penicillin, but in 72 it responded to streptomycin, in 78 to chloramphenicol, and in 79 to chlortetracycline. Of the 8 cases in which organisms other than staphylococci were isolated, these were sensitive to penicillin in 6. The treatment found most effective was local injection of streptomycin together with a 0.5% solution of procaine. In a further series of 303 children this form of therapy was successful in 81.2% of the 154 who received it. Good results were obtained in 75.4% of 65 children treated with procaine and penicillin, and in 54.5% of 44 children there was a satisfactory response to intramuscular injections of streptomycin and penicillin without procaine. In the cases in which these methods were ineffective, surgical intervention was necessary.

L. Firman-Edwards

1392. Suspected Hearing Defects in Phenylketonuria

S. W. LITTLE. *Archives of Otolaryngology* [Arch. Otolaryng.] 75, 515-518, June, 1962. 7 refs.

The author reports 2 cases, in a girl aged 2 and a boy aged 4, which were referred to him for investigation of suspected hearing defects. Both children were fair-haired, blue-eyed, and pale-skinned. Both had a marked gap between the upper central incisors and walked with a mild degree of incoordination. Plain audiometry showed that they could

hear reasonably well, but both of them showed evidence of mental retardation.

The combination of the physical appearance and mental retardation suggested a diagnosis of phenylketonuria, and this was confirmed by tests on the urine and blood. The author suggests that all children referred for the investigation of hearing defects should be subjected to a urinary screening test for phenylketonuria. C. O. Carter

1393. Acute Pulmonary Atelectasis in Infancy; Diagnosis and Pathogenesis in 63 Cases. (Le atelettasie polmonari acute nell'infanzia (considerazioni diagnostiche e patogenetiche su 63 casi))

P. L. FERRARI. *Acta paediatrica Latina [Acta paediat. lat. (Reggio Emilia)]* 15, 140-165, March-April [received July], 1962. 15 figs., 23 refs.

After briefly describing the anatomy of the normal lung, the author reports his findings in 63 young children with acute pulmonary atelectasis seen at the University Paediatric Clinic, Padua. The symptoms were variable, and diagnosis was impossible on clinical grounds alone. A table giving the incidence of signs and symptoms shows that cough and fever occurred slightly more often than any other clinical manifestation. The radiological diagnosis depends on the finding of an area of increased density corresponding to a segment of lung; there may also be emphysema or mediastinal displacement. Differential diagnosis from bronchopneumonia and atypical pneumonia is usually simple, since the radiological picture is different and the clinical signs in atelectasis are usually less marked. Segmental density may be present in tuberculous exudation and pneumonia, but these conditions differ clinically. There appear to be three distinctive modes of resolution in atelectasis, and these are described in detail. As regards pathogenesis, the author considers that in the majority of cases contraction of the smooth muscle of the lung is the major factor, and that this can cause atelectasis independently of bronchial occlusion. J. G. Jamieson

1394. The E.S.R. and Fractional E.S.R. in Infants with Pneumonia. (РЭ и ФРЭ при пневмонии у грудных детей)

V. D. SURKOV. *Вопросы Охраны Материнства и Детства [Vop. Okhrany Materin. Dets.]* 7, 27-31, July, 1962. 9 refs.

With a view to determining body reactivity in pneumonia, the author conducted certain investigations, including erythrocyte sedimentation rate (E.S.R.) and fractional E.S.R., in 118 infants (66 aged from 10 days to 3 months and 52 from 6 to 9 months) suffering from pneumonia and in 55 healthy infants. Fractional E.S.R. was determined according to Shteinberg's method, in which the sedimentation of the erythrocytes is recorded every 15 minutes for 2 hours, and a graph constructed with the falls in sedimentation and the time intervals as coordinates. The normal curve rises gradually to 45 or 60 minutes, then falls gradually; a shift of the peak to the left (that is, to 15 or 30 minutes) and a sharply pointed peak denote aggravation of the infection or supervening complications, while a shift of the peak to the right and flattening of its point indicate recovery. The E.S.R. levels were normal or only slightly raised in 65.6% of the younger group of infants with severe and acute pneumonia and in healthy children of corresponding age, and

in 56.2% of the infants over 6 months. As the children's condition improved, the proportion of normal E.S.R. values fell in the first group and rose in the second. In the convalescent period the E.S.R. rose and remained high in many children, but twice as frequently in the younger group. Many of the children with normal or slightly raised E.S.R. were suffering from toxæmia, abiotrophy, prematurity, dyspepsia, or otitis. This indicates, in the author's view, that the reactivity of the body to infection was depressed in the first months of life, especially in the presence of poor nutrition, rickets, or the complications mentioned. In most of the younger group of children the fractional E.S.R. was of the normal or hyporeactive type with low, wide peaks. Hyperreactive types predominated in the older group in children with acute or subacute pneumonia, or in toxic cases with complications; in these, as a rule, there was a raised E.S.R.

The author considers that at this early age the fractional E.S.R. is more valuable as a measure of the reactivity of the patient than of the severity of the infection, since the former often lags behind the latter and is slow in returning to normal after clinical recovery. L. Firman-Edwards

1395. Dynamics of the Fractional Erythrocyte Sedimentation Rate in Children with Pneumonia. (Фракционная реакция оседания эритроцитов в динамике патологического процесса при пневмонии у детей)

O. V. EMEĬ'ANOVA. *Вопросы Охраны Материнства и Детства [Vop. Okhrany Materin. Dets.]* 7, 31-34, July, 1962. 2 figs., 5 refs.

The author studied 100 children aged 6 months to 12 years who were suffering from various forms of pneumonia; the erythrocyte sedimentation rate (E.S.R.) and the fractional E.S.R. were carefully observed throughout the disease. The fractional E.S.R. was measured by Shteinberg's method, in which the sedimentation is recorded every 15 minutes for 2 hours and plotted on a graph with the time intervals as the abscissa and the sedimentation as the ordinate. The curve so obtained varies according to the reactivity of the patient, who is described as hyperreactive, reactive, normal, hyporeactive, or areactive. A shift of the peak to the left and sharp angulation suggest a severe infection, an exacerbation of the disease, or complications, while a shift to the right and flattening of the peak indicate recovery. Most of the children with lobar or focal pneumonia were hyperreactive, while those with small, disseminated patches were reactive or hyporeactive. The observations were repeated several times on each patient throughout the illness (a total of 225 times on the 100 children) and gave a clear picture of the progress of the disease and of the patient's reactivity.

[Most of these children were older than those investigated by Surkov (see Abstract 1394). The technique of the fractional test was devised by Panchenko and the scheme of classification by Shteinberg.] L. Firman-Edwards

1396. Chronic Hepatitis with Hypergammaglobulinemia in Childhood: Report of Eight Cases

A. GROSSMAN, I. M. ROSENTHAL, and P. B. SZANTO. *Pediatrics [Pediatrics]* 29, 933-947, June, 1962. 5 figs., 24 refs.

The authors report on 8 children with chronic hepatitis and marked hypergammaglobulinaemia seen at Cook County Hospital, Chicago. The series comprised 6 females

and 2 males, whose ages at the time of onset ranged from 7 to 15 years. Jaundice, hepatosplenomegaly, and a history of epistaxis were present in each case; 6 of the patients had skin manifestations, and 7 complained of arthralgia. The laboratory investigations revealed in all the cases: rise in serum globulin level with marked increase in γ -globulin; raised bilirubin concentration in serum; abnormal cephalin flocculation and thymol turbidity; depressed prothrombin times. The result of the "bromsulphalein" retention test was abnormal and the level of glutamic-oxalacetic transaminase in the serum was markedly raised in all the cases in which these tests were performed. In none of the cases was the serum cholesterol concentration raised. The levels of alkaline phosphatase were raised in 5 cases and normal in 3.

Treatment in all cases was with adrenocortical steroids; 5 patients improved and 3 died. Necropsy showed post-necrotic cirrhosis in all of the 3 fatal cases. The authors stress that the symptoms and laboratory findings in this series do not appear to differ significantly from those in adults, and they consider that chronic hepatitis with marked hypergammaglobulinaemia in childhood is not a separate disease, but should be classified with similar cases occurring in adults. There is evidence that autoimmunization against hepatic tissue may be an important factor in pathogenesis, but this has not been proved. Although none of these cases of chronic hepatitis with hypergammaglobulinaemia had a positive L.E.-cell test, this condition is perhaps related to disseminated lupus erythematosus and to chronic hepatitis with a positive L.E.-cell test.

R. G. Meyer

✓ 1397. **Antibiotic Treatment of Infant Enteritis with Humatin.** (Die antibiotische Behandlung der Säuglingsenteritis mit Humatin) S. SEIDL. *Medizinische Klinik [Med. Klin.]* 57, 1010-1013, June 8, 1962. 30 refs.

At the Paediatric Clinic of the Free University of Berlin the author treated 37 infants suffering from infectious enteritis with paromomycin ("humatin"), an antibiotic of low toxicity derived from *Streptomyces rimosus* var. *paromomycinus*. It acts locally on the intestine, not being absorbed from the gastro-intestinal tract. It is most active against *Escherichia coli*, but has a bacteriostatic or bactericidal action on *Shigella*, *Salmonella*, *Proteus*, and staphylococci. It may have been its antistaphylococcal effect which, in the author's series, prevented the post-antibiotic complications of staphylococcal enteritis. The author found the optimum daily dosage to be 30 to 50 mg. per kg. body weight, which he gave divided in 4 doses for 5 to 6 days.

There was rapid improvement in the general condition of all the patients. Infants began to take their feeds again, and within 3 to 4 days their stools became normal in frequency, consistency, and bacteriology. There were no side-effects. Because of the severity of the enteritis, babies were treated with diet in addition to paromomycin and this made exact assessment of the value of the drug more difficult. Among 140 strains of *E. coli* tested, only 2, O111 and O127, were resistant to paromomycin. Resistance to an antibiotic, the author points out, depends on the frequency with which it is used and on the strain of the organism present. Hitherto, in Germany, neomycin has been the antibiotic to which least resistance has developed and O111 and O119 the strains of *E. coli* with the greatest resistance to streptomycin,

chloramphenicol, and tetracycline. He welcomes paromomycin as a new drug for the treatment of enteritis in infants.

E. S. Wyder

1398. **The Treatment of Enuresis by Isopropamide, a New Synthetic Drug Acting on the Parasympathetic System.** (Du traitement de l'énurésie par un nouveau parasympatholytique de synthèse, l'isopropamide) J. P. CHRISTEN. *Praxis [Praxis]* 51, 745-748, July 19, 1962.

The author reports on the treatment with isopropamide of 26 children with enuresis at La Chaux-de-Fonds, Switzerland. Isopropamide, a synthetic parasympatholytic drug, is a quaternary ammonium base of 2:2-diphenyl-4-diisopropylaminobutyramide, with an anticholinergic action 4 times that of atropine. It is non-toxic, and in therapeutic doses is well tolerated by infants. The author recommends 20 drops of isopropamide at night for nocturnal enuresis, and 10 drops morning and night for diurnal and nocturnal enuresis. His series consisted of 11 girls and 15 boys aged between 2½ and 16 years, 20 with nocturnal enuresis, 2 with diurnal enuresis, and 4 with both diurnal and nocturnal enuresis. The duration of treatment varied from 15 days to 6 months. Complete cure was obtained in 11 children, in 2 the diurnal but not the nocturnal enuresis was cured, in 6 there was improvement, and 7 failed to respond. The author comments that since enuresis has several causes, no single drug can be expected to be successful in every case and that isopropamide is the most satisfactory drug he has so far encountered.

E. S. Wyder

1399. **Eczema Vaccinatum Treated with N-Methylisatin β -Thiosemicarbazone**

W. TURNER, D. J. BAUER, and R. H. NIMMO-SMITH. *British Medical Journal [Brit. med. J.]* 1, 1317-1319, May 12, 1962. 2 figs., 5 refs.

A trial of N-methylisatin β -thiosemicarbazone (33T57) in the treatment of eczema vaccinatum is reported. In a 7-month-old child in whom infantile eczema had been successfully treated with a "steroid cream" two pustules appeared on the scalp following successful vaccination of his parents. Within 3 days typical vaccinia lesions appeared all over the child's scalp and became confluent. The lesions spread to the shoulders, arms, and legs. There was marked oedema of the scalp and the child became very ill, with pyrexia, prostration, and toxæmia. Antibiotics and hyperimmune γ -globulin had no effect. The child was given 33T57 by mouth in a dosage of 250 mg. every 6 hours. After 3 days there was a sudden improvement in the general condition, no further pustules developed, and the existing pustules dried up with little scarring.

A week after treatment with 33T57 was instituted the child developed severe gastroenteritis. The drug was withdrawn but the symptoms did not abate until the patient had had intravenous medication and feeding for 3 weeks. Since several patients in the ward had severe gastroenteritis at the material time the child probably had a cross-infection, but the possibility of the condition being a side-effect of 33T57 cannot be ruled out.

An extinction curve of a toluene extract of the patient's plasma suggested that an effective concentration of the drug was attained by the second day. The altered shape of the curve also suggested that some metabolic change had occurred.

E. H. Johnson

Medical Genetics

1400. **Clinical Assessment of Lathyrism as a Familial Disease.** (Aportación clínica de latirismo como enfermedad familiar)

E. ROMERO and E. F. MARCOS. *Revista clínica española* [Rev. clín. esp.] 85, 270-275, May 31, 1962. 1 fig., 41 refs.

This is an account, from the University of Valladolid, Spain, of lathyrism in a family which, since January, 1947, had fed mainly on vetch. The disease appeared early in April of that year in 5 of the 7 children aged between 11 and 22 years. Vetch was then eliminated from the diet, but the remaining 2 children were affected a month later, although in them the condition was mild and recovery was complete. The prodromal symptoms were fatigue of the limbs and urgency of micturition. Weakness of the legs rapidly increased, until by the tenth day the patients could not walk without support. The paresis then began to improve and sphincter control was regained. The clinical findings at the time the paper was written were those of a pyramidal lesion situated between the ninth and twelfth dorsal segments of the spinal cord, loss of upper or lower or of both upper and lower abdominal reflexes, spastic paresis of the legs, increased knee and ankle jerks, bilateral knee and ankle clonus, bilateral extensor plantar responses, and loss of the cremasteric reflex. The gait was abnormal, with dragging of the feet and limping. Romberg's sign was not present. There were no other abnormal findings, and in particular no sensory or sphincter disturbances.

The authors reject the view that lathyrism is caused by the simple action of a neurotoxin present in the vetch, or by malnutrition and consequent lack of a factor which normally neutralizes the vetch neurotoxin, or by a virus present in vetch. They maintain that the condition is the result of a toxic action superimposed on a pre-existing genetic enzymopathy of the nervous tissue of the pyramidal system. According to this theory genetic alteration of one of the enzymes biologically essential for the metabolism of the pyramidal system is usually fully compensated by neighbouring enzymes, but the presence of some toxic factor contained in vetch precipitates the clinical manifestation of lathyrism by attacking the pyramidal system and, possibly, its metabolism.

T. A. Pace

1401. **Sex Determination by the Form of the Neutrophil Granulocyte Nucleus.** (Об определении пола по форме ядра нейтрофила)

S. I. RJABOV. *Проблемы Эндокринологий и Гормонотерапий* [Probl. Endokr. Gormonoter.] 8, 93-97, May-June, 1962. 7 figs., 15 refs.

Several workers have shown that nerve cells, cells of the internal organs of female animals, and the neutrophil granulocytes of the blood contain in their nuclei distinct nucleoli peculiar to their sex. Davidson and Smith (*Brit. med. J.*, 1954, 2, 6; *Abstr. Wild Med.*, 1955; 17, 6) found that in over 2% of the neutrophil granulocytes of women this nucleolus is in the form of a projection shaped like a drumstick. The present author repeated these observations with the object of determining: (1) the extent to which such a definite sex-chromatin pattern exists; (2) how far it is related

to the blood oestrogen level; and (3) how far it may be affected by excess of other hormones, especially those of the hypophysis and adrenal glands.

Blood films taken from 100 healthy men and women (50 of each sex) and from 33 women with various endocrine disorders were prepared and stained by the method of Davidson and Smith, and 500 neutrophil granulocytes examined in each film. Three types of separate nucleoli were identified—the "drumstick", the "sessile nodule", and the "small club". The last, small projections in the form of a thread or hook, were most common in the neutrophil granulocytes of men, and were often multiple. Some of them were of the same shape as the "drumsticks", but were smaller and had a clear centre. No female blood contained fewer than 6 neutrophils with "drumsticks" out of 500; only 6 men had any of these, and no man had more than 2 per 500 cells. A "drumstick" count of over 6 in 500 neutrophils is therefore regarded as diagnostic of the female origin of the blood. Age, and therefore, presumably, oestrogen level, had no effect on the numbers found in women. The findings as regards the other types were less uniform, but "sessile nodules" were commoner in women and "small clubs" in men. The level of oestrogens and other hormones in cases of acromegaly, Cushing's disease, Addison's disease, and other endocrine disorders had no effect on the incidence of "drumstick" formation.

L. Firman-Edwards

1402. **A Hereditary Anomaly of the Oculomotor Apparatus.** (Наследственная аномалия глазодвигательного аппарата)

V. A. REUTOVA and A. I. KOROEV. *Журнал Невропатологии и Психиатрии* [Zh. Neuropat. Psikhlat]. 62, 657-679, No. 5, 1962. 2 figs., 2 refs.

A study is reported, from the Medical Institute of Orjoni-kidze, of 6 generations of a family, some of whose members suffered from an abnormality of the oculomotor apparatus. Data were obtained from examination of patients, from photographs, and from verbal descriptions from older members of the family. Affected members are born with the anomaly, which seems to be very uniform in type. There is bilateral ptosis, but the ability to close the eyes is preserved. The eyes are directed downwards and no voluntary movement of them is possible, except that the attempt to move them towards one or other side causes them to converge. There is no diplopia and, apart from amblyopia in some cases, the eyes themselves are healthy. Pupillary reaction to light is preserved. An occasional finding is slight facial asymmetry. The ptosis and absence of eye movement are compensated by backward and rotatory movements of the head. The condition is non-progressive and those affected are otherwise healthy. The sexes are affected in equal numbers. The condition is transmitted only by affected subjects. Only one affected female married and her only daughter is unaffected. A branch of the family arising from an unaffected male was traced and found to have been unaffected for 5 generations.

[The authors do not speculate on the genetic mechanism involved.]

G. P. McGovern

Public Health and Industrial Medicine

1403. **Endemic Fluorosis.** (An Epidemiological, Biochemical and Clinical Study in the Bhatinda District of Panjab)

A. SINGH, S. S. JOLLY, P. DEVI, B. C. BANSAL, and S. S. SINGH. *Indian Journal of Medical Research* [Indian J. med. Res.] 50, 387-398, May, 1962. 6 figs., 11 refs.

This paper from the Medical College, Patiala, and the Central Research Institute, Kasauli, gives an account of a field survey of endemic fluorosis in 13 villages and towns of the Bhatinda district of the Punjab, where the fluorine content of drinking-water varies from 0.3 to 16.2 p.p.m. and that of the soil from 2.27 to 8.5 mg. per 100 g. The survey was based on a chemical examination of those inmates of every tenth house who were over 30 years of age, since the presence of skeletal fluorosis presupposes approximately 20 years of continuous exposure to fluorine. A sample of 2,282 persons was examined in this way out of a total population of approximately 58,000.

Skeletal fluorosis was diagnosed in 63 persons (52 male and 11 female) who underwent detailed clinical, radiological, and pathological examination. The signs and symptoms were pains in the back, shoulder, and neck, stiffness, and deformities. Radiography showed bony changes consisting of ridging, tuberosities, abnormal bony deposition, osteosclerosis, and calcification of ligaments, tendons, and interosseous membranes. Bone biopsy revealed excessive quantities of fluorine in the bone ash ranging from 60 to 680 mg. per g., with an average of 217 mg. per g. Neurological complications were found in 27 cases, the commonest being a spastic paraplegia or quadriplegia with upper motor neurone involvement in the lower limbs and evidence of root compression in the upper limbs. Routine analysis of urine and blood, as well as kidney function tests, gave normal results. The fluorine content of the blood varied from 0.06 to 1.45 mg. per 100 ml. and that of urine from 0.175 to 2.19 mg. per 100 ml. A separate examination established the presence of dental fluorosis in 67% of 786 school-children.

The authors discuss the social and preventive aspects of his problem, and advocate the use of canal water from the Punjab irrigation scheme for human consumption since this water has a fluorine content of less than 1 p.p.m.

T. A. Pace

404. **A Live Vaccine Against Q Fever.** (Проблема живой вакцины против лихорадке Ку)

P. F. ZDRODOVSKI and V. A. GENIG. *Вопросы Вирологии* [Vop. Virus.] 7, 355-358, May-June, 1962. 2 figs., 8 refs.

Although killed vaccines of *Rickettsia burneti* produce satisfactory immunity, they have the disadvantage of causing local infiltrations and sometimes abscesses. A spontaneously occurring non-pathogenic variant of the "Grita" strain, labelled M-44, has been studied with a view to its suitability for preparing a living vaccine. Strain M-44 is non-pathogenic for guinea-pigs and dies out after 7 to 8 passages through guinea-pig testicles. It is also non-infectious for guinea-pigs under intensive cortisone medication.

However, its infectious capacity is unaltered in chick embryos, and 1 ml. of chick embryo culture, diluted 10^{-4} , produced well-marked immunity in guinea-pigs against infection with high doses of the virulent parent strain. After 3 to 7 days immunized guinea-pigs were immune against 1,000 infectious doses and after 45 days against 100,000 to 500,000 infectious doses.

On the basis of these experimental data it was decided to immunize 79 volunteers aged 11 to 55. Of these, 52 gave a negative complement-fixation reaction, 13 had been vaccinated once previously, and 14 had been revaccinated 4 years after primary immunization. The living M-44 vaccine was given in a dose of 0.5 ml. embryonated egg culture reconstituted from the freeze-dried state. Of the 52 previously unvaccinated persons, 10 had a slight general reaction 2½ days later and 12 had a slight local reaction after 3 days. No rickettsiae could be isolated from the blood of any subject on the 6th, 9th, 11th, 13th, and 17th days. Of the 13 subjects vaccinated once, 4 had a short-lived general reaction on the third day and also a fleeting local reaction; probably due to the previous sensitization. Complement-fixation titres began to rise from the 21st day from 1 in 20 to 1 in 84, and reached a maximum of 1 in 160 within 60 days. When a combination of the live M-44 vaccine with the E strain of *R. prowazeki* was tried in 25 volunteers, slight reactions occurred in only 2. Recently the M-44 vaccine has been used together with the 19-WA *Brucella* strain, again without serious side-effects. Strain M-44 is therefore now to be tried in a large epidemiological experiment approved by the Soviet Ministry of Health.

K. Zinnemann

INDUSTRIAL MEDICINE

1405. **Micro-cinematographic Phase-contrast Study of the Phagocytosis of Diatomite Dusts.** (Étude microcinématographique en contraste de phase de la phagocytose des poussières de diatomite)

A. POLICARD, A. COLLET, and J. C. MARTIN. *Archives des maladies professionnelles, de médecine du travail et de sécurité sociale* [Arch. Mal. prof.] 23, 329-331, June, 1962. 8 figs.

Direct microscopy of histological preparations, including photomicrographic slides suitable for projection, has hitherto served mainly for the study of the anatomical structure of cells and tissues. Phase-contrast microcinematography has now enabled morphological examination to be supplemented by observations on physiological and physiopathological cell reactions under various conditions, and particularly in relation to foreign dust particles.

In a study at the Centre d'Études et Recherches des Charbonnages de France, Verneuil-en-Halatte (Oise), rats were injected intraperitoneally with a suspension of diatomite dust of particle size under 3μ . The diatomite had not been subjected to heat or chemical treatment and therefore, as expected, behaved as an inert dust. After 21 to 48 hours the animals were killed and the peritoneal exudate was

examined microscopically. The cell reactions to the dust were recorded by a ciné-camera coupled to the microscope, and this made possible the observation of reactions and changes beyond the scope of previous methods. The changes observed included the different phagocytosing capabilities of mononuclear cells, histiocytes, and polymorphonuclear leucocytes, and vacuole formation in the cell protoplasm.

The authors recognize that the present experiment represents no more than a pilot exercise. The importance of the report is that it directs the attention of research workers to the potentialities of this new tool in the study of the pneumoconioses at cell level. The paper is illustrated by an excellent series of 8 plates with explanatory text.

A. Meiklejohn

1406. **The Respiratory Apparatus in Sulphur Miners.** (L'apparato respiratorio nei minatori di zolfo)

A. GUARINÒ, R. MOLE, and G. SESSA. *Folia medica* [*Folia med. (Napoli)*] 45, 461-479, June, 1962. 5 figs., 17 refs.

Writing from the University of Naples, the authors recall the modern view that bronchopulmonary disease in sulphur miners (primarily a chronic dry bronchitis of spastic type often associated with emphysema) is more probably due to the repeated toxic action of sulphur dioxide (SO_2) than to any pathogenic action of sulphur powder. At the sulphur mines of Avellino they examined 380 workers, 210 of whom worked underground in an 8-hour shift 6 days a week, 120 worked at the surface at crushing, milling, refining, and packaging, 30 were craftsmen, and 20 were managerial and clerical staff. Of the whole group, 80% complained of irritating cough, often with some sputum and pain in the chest, sometimes slight fever, and, in 32%, dyspnoea on exertion. Clinical examination showed abnormal physical signs in the chest—rhonchi or rales and diminished movement at the bases—in 55% of the patients; although these signs were present primarily in those "getting" the sulphur they were also found in the surface workers, almost all of whom had worked for several years underground and had been put on surface work only because of their general or cardiorespiratory condition. The remaining staff had practically no respiratory lesions. All the underground workers stated that they had been repeatedly exposed to the inhalation of SO_2 , and in 12% these exposures had caused them to be admitted to hospital.

Radiological examination of the chest and spirometry were carried out in 45 of these workers, the respiratory function tests being designed to assess both the static and dynamic volumes. Respiratory function was normal in 16 patients, in 6 there was slight respiratory deficiency, in 12 definite respiratory deficiency with increased residual volume (R.V.), and in 8 a global respiratory deficit, 6 having in addition an increased R.V. In 16 the x-ray appearances were normal; in the remainder lung markings were increased in all fields, often with hilar thickening; 2 patients had micronodulation with striae in the perihilar areas and in the middle zones, but no evidence of reticulation; in 2 there was increased transparency in one or more fields, especially at the bases. No silicotic lesion was found. One patient had bilateral subclavicular infiltration with right-sided cavitation and 3 had a primary complex. In 15% of the subjects there was no history of chest symptoms, yet x rays showed slight pleural thickening or partial obliteration of the costophrenic angle; this was ascribed to circumscribed

pleurisy resulting from contiguity with small, rapidly resolving bronchopneumonic foci near the visceral pleura. Chronic bronchitis, almost always accompanied by emphysema, was present in 51% of the patients. The mildest lesions were seen in patients under 40 years of age, although there was no parallel between length of exposure to risk and the severity of the lesions. The authors attribute the special frequency of respiratory disease in sulphur workers to various causes, including dusty conditions (especially underground), high concentrations of SO_2 (particularly after shot-firing), high humidity, and very rapid changes of temperature when coming off shift. Technical improvements are suggested which would reduce the incidence of these conditions.

W. K. Duncombe

1407. **Occupational Dermatitis, with Special Reference to Forms Associated with the Sulphur Industry.** (Dermopatie professionali con speciale riguardo alle forme inquadabili nella tecnopatia solforosa)

V. GRAMIGNANI and G. GRIMALDI. *Folia medica* [*Folia med. (Napoli)*] 45, 491-503, June, 1962. 2 figs., 10 refs.

The authors, writing from the Institute of Industrial Medicine of the University of Messina, state that an important aspect of occupational dermatitis is so-called crossed sensitivity through primary and secondary allergens; the greater the degree and frequency of contact with the primary allergen, the greater is the tendency to the development of crossed sensitivity to additional substances. The practical importance of this is that substances which do not usually cause dermatitis may have a sudden and marked effect on the skin. Thus a single chemical substance, or one type of work, may cause several skin conditions, while different substances may cause identical symptoms. This multiform effect is well illustrated in sulphur workers.

Between 1953 and 1957 1,488 cases of occupational dermatitis were seen at the Catania Dermatology Clinic; 23 were in sulphur workers, and 2 are described in detail. The first patient, a man who had worked with sulphur for 16 years, complained of intensely itchy, sometimes exudative, erythematous spots over the whole body, but more especially on the back, scrotum, and limbs. They regressed if the patient left off work, only to begin again when he resumed it. Examination 2 years after the first complaint revealed, in the lumbar and gluteal regions, reddish spots with fine vesiculation alternating with zones of reddish nodules of the size of a pin-head and crusty erythematous spots and thickening of the skin. On patch-testing with an ointment containing 5% of finely powdered sulphur in a lanoline base, an erythematous area with vesiculation 3 cm square appeared at the test site after 72 hours together with similar lesions on the side of the chest and on the shoulders. When the test was repeated 16 days later similar change occurred, while in control subjects the tests gave negative results.

The second patient had worked with sulphur for nine years (with some interruptions) but had given up this work in 1953 because of itchy erythema and oedema which had appeared the year before, first on the face, then spreading to the whole body. When he stopped working with sulphur the condition improved. In 1959 the skin was red and oedematous, with small spots of pityriasis and moderate thickening with hyperaemia and lichenization of the hands, scrotum, and inguinal regions. In 1961 there were slight erythema and desquamation of the skin of the face, hands

scrotum, and inguinal areas, and the reaction to a patch test was negative. Clinical and radiological examination of the chest showed mild chronic bronchitis in both patients. The negative patch-test reaction in the second case is attributed to the facts that the reaction is not necessarily positive even in frankly occupational cases and that the patient had given up his work some years before. Discussing the diagnostic and medico-legal aspects of occupational dermatitis, the authors state that, in addition to skin diseases which are actually caused by certain occupations, there are others which may be secondary and which, though clearly occupational, may not qualify for compensation. Certain skin manifestations may be of a transient or episodic nature; or there may be sensitization which, if induced, may involve some permanent invalidism. Only exceptionally is the skin the sole organ affected in sulphur workers, and the investigator should look for changes in other parts of the body. Careful selection is necessary to eliminate from such work persons who have any known hypersensitivity.

W. K. Dunscombe

1408. Frequency of Peptic Ulcer among Executives, Craftsmen, and Foremen

J. P. DUNN and S. COBB. *Journal of Occupational Medicine* [J. occup. Med.] 4, 343-348, July, 1962. 2 figs., 19 refs.

The authors examine the prevalent concept that the executive in industry is "the prime candidate" for peptic ulcer. After reviewing the literature they describe the results of an investigation into the gastro-duodenal health of 377 executives, 273 craftsmen, and 34 foremen carried out at the Graduate School of Public Health, University of Pittsburgh, Pennsylvania, by means of a questionnaire and by estimation of gastric function on the basis of the serum pepsinogen level. The pepsinogen concentration of the blood is expressed as μg . of tyrosine per ml. of serum.

The questionnaire contained three main indices: (1) the occurrence of pain in the stomach 2 hours after eating and relieved by milk or food; (2) pain in the stomach awakening the subject from sleep at night; and (3) a positive history of peptic ulcer as proved by x-ray examination. Considering only those subjects who gave a positive reply to all three questions and regarding the frequency of this response in executives as 1, the frequency for craftsmen was 1.38 and that for foremen 7.40. If only subjects who had undergone gastrectomy are considered, the frequency in executives again being taken as 1, the rate for craftsmen was 1.38 and that for foremen 11.03.

The mean pepsinogen level was highest in the executives (632 μg . per ml.), and there was little difference between the figure determined for craftsmen (564 μg . per ml.) and that for foremen (534 μg . per ml.). Detailed scrutiny of each group, however, revealed that the serum pepsinogen level increased steadily with the number of positive indices, and that in craftsmen who had a serum pepsinogen value above 800 μg . per ml. the incidence of peptic ulcer was six times greater than in craftsmen in whom the level was less than 500 μg . per ml.

These findings are discussed and it is concluded that peptic ulcer is more common and also more severe in foremen than in either executives or craftsmen. No evidence was found to support the view that executives are especially prone to peptic ulceration. It is suggested that determination of the serum pepsinogen level may have "some predictive value" in this context.

M. A. Dobbin Crawford

1409. Δ -Aminolaevulinic Acid in the Serum and Urine in Lead Poisoning. (L'acido Δ -amino-levulico serico ed urinario nell'intossicazione saturnina)

L. RASETTI and A. PARIGI. *Folia medica* [Folia med. (Napoli)] 45, 480-490, June, 1962. 4 figs., 4 refs.

In this paper from the University and the Ospedale Mauriziano, Turin, the authors point out that, as a result of changes in industrial techniques together with better preventive measures, atypical forms of lead poisoning, giving rise to difficulty in diagnosis, have become increasingly frequent in recent years. Although many tests are used in the diagnosis of lead poisoning, the inconsistency of their results suggests that the various changes in the blood chemistry are not all due to the same cause. The authors made a special study of the metabolism of 2 porphyrin precursors, porphobilinogen (PBG) and Δ -aminolaevulinic acid (ALA); in 20 men working with an alloy of lead and tin used in finishing car bodies. The following investigations were carried out: erythrocyte count, stippled cell count, haemoglobin determination, determination of lead in blood and urine, assay of coproporphyrin, free porphyrin in the erythrocytes, plasma PBG and ALA levels, and the daily excretion of coproporphyrin, PBG, and ALA. The erythrocyte count was less than 4,000,000 per c.mm. in 7 patients, the proportion of stippled cells was significantly increased in 3, the blood lead concentration was above normal in 14, and the urinary lead concentration above normal in 18. There was no significant variation in erythrocyte coproporphyrin content, blood PBG level, or PBG excretion; the erythrocyte protoporphyrin content was markedly increased in 17 cases and the urinary coproporphyrin content in 18. The mean plasma ALA level and the mean ALA excretion were nearly 3 times the normal average. According to the authors it is the synthesis of PBG from ALA and the incorporation of iron into protoporphyrin that are most affected by lead, even in very low concentrations, and the high blood and urinary levels of ALA are due to blockage by lead of the enzyme ALA-dehydrase. The appearance of a high plasma ALA level and increase in the erythrocyte protoporphyrin content are very early signs of lead poisoning. The investigation of blood and urinary levels of ALA is thus preferable to other laboratory tests because of the significance and consistency of the findings and the speed and simplicity with which the tests can be performed; the assay technique enables the PBG content of the blood and urine to be estimated at the same time and toxic porphyria thus to be distinguished from hepatic porphyria.

The authors stress the important practical point that in lead poisoning anaemia may be slight or absent, even in the presence of severe disturbance of the porphyrin picture and high blood and urinary levels of lead. The stippled cell count also may disagree with the results of other laboratory tests. In the authors' cases estimation of the lead concentration in the blood was the least valuable of all the tests, since in 5 cases it was normal although signs of saturnism were evident. Discrepancy of this type has never been noted with plasma ALA assay, the results of which have always corresponded with the presence and gravity of lead poisoning. The authors consider that estimation of the plasma ALA content is the simplest and, relatively, the most accurate method of detecting saturnism, although for a complete picture where the diagnosis is doubtful the usual full battery of tests may be needed.

W. K. Dunscombe

Forensic Medicine and Toxicology

1410. Identification of the Pseudocholinesterase Type in Human Blood Spots

H. LEHMANN and D. DAVIES. *Medicine, Science and the Law* [Med. Sci. Law] 2, 180-183, April, 1962. 3 refs.

The authors describe, from St. Bartholomew's Hospital, London, a method for classifying dried blood stains according to the type of pseudocholinesterases present in them. These enzymes are identified by an inhibition technique involving the use of the local anaesthetic dibucaine (cinchocaine), a percentage inhibition figure called the dibucaine number (D.N.) being arrived at. The pattern in each individual is determined by gene inheritance; the great majority of persons are homozygous for the usual enzyme and have a D.N. of about 80. Less than one person in 1,000 is homozygous for an unusual pseudocholinesterase having a D.N. of about 20, while one person in 35 is heterozygous for both enzymes and has a D.N. of roughly 38. It is stated that the enzyme pattern of a blood spot which has been kept dry, as expressed by its dibucaine number, is reasonably constant and may occasionally be of use in forensic practice.

Gilbert Forbes

1411. Blood Lavage in Acute Barbiturate Poisoning: Ten Years' Experience

W. T. L. OHLSSON and B. I. FRISTEDT. *Lancet* [Lancet] 2, 12-16, July 7, 1962. 3 figs., 28 refs.

A total of 605 cases of acute barbiturate poisoning, severe in 76, moderately severe in 215, and mild in 314, treated by blood lavage at the Central Hospital, Örebro, Sweden, are reported. Since cases designated "severe" were those in which coma lasted over 24 hours after admission to hospital, their low proportion may be evidence of the efficacy of the treatment.

The barbiturates commonly taken were amylobarbitone, phenobarbitone, or a combination of butabarbital sodium and aprobarbital sodium. The concentration of barbiturate in the blood varied between 4 and 10 mg. per 100 ml., but in one case it was 31.3 mg. per 100 ml. Treatment consisted in administration of oxygen and forced diuresis by intravenous infusion of "macrodex" (a dextran preparation), Ringer's solution, and 5% glucose solution. The fluid balance was controlled by measurement of the quantity and specific gravity of the urine excreted through a retained catheter. An outflow of 15 to 20 drops per minute was held to indicate normal circulation and kidney function. A mercurial diuretic (mersalyl) was then given and the speed of infusion increased to that of the urine flow. When needed, the diuretic was repeated in 17 to 20 hours. On average, 0.3 litre was infused every hour, or 7.2 litres per 24 hours, with a diuresis of 0.2 litre per hour, or 4.8 litres per 24 hours. In severe cases up to 10 litres per 24 hours was given with urine excretion of 7 litres per 24 hours. Bemegride was found useful where unconsciousness was due to barbiturate alone, but less so where anoxia had supervened, and here analeptics are probably contraindicated. Occasionally drugs were used to raise the blood pressure. Antibiotics were given for prophylaxis of infection. The

temperature on admission was commonly subnormal, the lowest recorded being 82.4° F. (28° C.) 12 hours after admission. With lightening of the coma there was a brief rise in temperature to not more than 100° F. (37.8° C.). The airway being maintained, oxygen was given in a hood in which the temperature was 70° F. (21.1° C.) and the relative humidity 60 to 70%. The carbon dioxide content was kept below 1% and the oxygen about 60%, but this was adjustable to 100% at need; 25 to 30 litres of the mixture per minute was delivered, through the hood. The head was kept low, at a 15-degree tilt, to relieve the lungs and aid the bronchial toilet. Intubation was not practised, because of the risk of shifting or of blockage of the tube. Tracheostomy was performed in 21 cases. The average duration of coma was 58 hours in the severe and 10 hours in the moderately severe cases; it was prolonged if the patient arrived in a state of shock or if delay in reaching hospital had resulted in anoxia. Tolerance was observed in drug addicts and in epileptics under barbiturate therapy, consciousness returning while the blood barbiturate content was still high. Treatment was stopped as soon as the patient began to move spontaneously and was able to swallow.

This method of blood lavage can be used only where the circulation and the kidney function are normal. In no case was there any sign of acute pulmonary oedema, which was probably prevented by the increased salt excretion produced by the mercurial diuretic. In no case was renal insufficiency the cause of death. In the deeply comatose, the urea clearance was reduced but there was no oliguria. There were 14 deaths (2.3%); in 7 of these cases blood lavage had not been used, on account of kidney or heart disease; in 11 cases death was due to bronchopneumonia, combined in 2 cases with heart disease, in one it was due to heart disease alone, and in 2 to unknown factors. The laboratory tests are listed and the nursing measures given in detail, with records of one patient in whom coma lasted for 97 hours.

The advantages over other methods of treatment are: (1) consciousness returns more quickly, (2) shock is reduced or prevented, and there is therefore less need for drugs to raise the blood pressure, (3) there are no renal complications, (4) there is no hyperthermia, and (5) crusts are less likely to form in the respiratory passages.

M. A. Dobbin Crawford

1412. Fatal Intoxication with Isopropyl Alcohol (Rubbing Alcohol)

L. ADELSON. *American Journal of Clinical Pathology* [Amer. J. clin. Path.] 38, 144-151, Aug., 1962. 16 refs.

The author describes 5 fatal cases of isopropyl alcohol poisoning seen over a recent 7-year period in Cleveland, Ohio. In all cases there was a very deep coma with absence of reflexes, which generally persisted until death. Other symptoms included haemorrhagic pulmonary oedema and gastritis; acetonuria was always present. The author states that excretion is by the stomach, salivary glands, and kidney, and that treatment should include repeated or continuous gastric lavage to stop reabsorption. Oxygen should also be given, by intratracheal tube if necessary. V. J. Woolley

Anaesthetics

1413. Electronic Instrumentation in Routine Anaesthetics: a Combined Cardio-tachometer, Drip-rate Counter and Thermometer

E. R. FAWCETT, D. R. MCCALLUM, and R. INGLES. *New Zealand Medical Journal* [N.Z. med. J.] 61, 219-223, April, 1962. 2 figs.

A transistorized unit for measuring pulse rate, temperature, and rate of intravenous drip infusion during operation is described as an instrument which should be available for routine use. It is a cube of 6 in. (15.2 cm.) standing on the tray of a Boyle's anaesthetic trolley. Pulse rate is recorded by needle electrodes from the QRS complex of the electrocardiogram (Lead II) and each beat is shown by a movement of the needle on an ammeter scale and by an audible "bleep". Each drop of fluid dripping through the drip-chamber of the infusion apparatus passes before a light source, and the alteration of intensity of light is similarly recorded by means of a phototransistor probe, using the same ammeter. The ammeter scale is also calibrated in degrees centigrade (10° to 30° C. and 25° to 45° C.) so that body temperature measured by a thermistor probe can be read directly. Any of these parameters can be measured by selecting the appropriate input.

D. D. C. Howat

1414. The Amnesic Properties of Hyoscine and Atropine in Pre-anaesthetic Medication

T. K. HARDY and D. WAKELY. *Anaesthesia* [Anaesthesia] 17, 331-336, July, 1962. 10 refs.

A comparative study of the amnesic properties of hyoscine and atropine when used in customary clinical dosage before anaesthesia was carried out at the Royal Infirmary, Cardiff, on 200 patients undergoing minor surgery under anaesthesia with thiopentone, nitrous oxide and oxygen, and either trichlorethylene or halothane. One-half of the patients, selected at random, were premedicated with atropine and one-half with hyoscine administered subcutaneously, the dosage being on the basis of 0.6 mg. of atropine and 0.4 mg. of hyoscine per 10 stone (64 kg.) body weight. In addition, all patients had morphine preoperatively. Immediately before the induction of anaesthesia the patient was shown a single-line drawing of one of 5 common objects and asked to name it, the order of exhibition to successive patients being varied at random. At a time when the effects of anaesthesia could be expected to have worn off—that is, 6 to 12 hours after operation—the patient was asked if he remembered seeing a picture and, if so, which picture he had seen. Of the 100 patients who received hyoscine, 7 had no memory of the picture, whereas all patients given atropine remembered the drawing. A further 6 members of the former group, although remembering the picture, had some amnesia for preoperative events, as had one patient who received atropine. The results are briefly discussed and it is concluded that "although hyoscine was found to possess amnesic properties significantly greater than atropine, the results failed to justify the marked reputation at present enjoyed by hyoscine for the production of amnesia".

Mark Swerdlow

1415. Clinical Comparison of Thiopentone and Methohexitone

J. G. WHITWAM and J. M. MANNERS. *British Medical Journal* [Brit. med. J.] 1, 1663-1665, June 16, 1962. 20 refs.

A comparative study of the efficacy of two anaesthetic agents, thiopentone and methohexitone, is reported. The drugs were given alternately to 100 male and 50 female patients attending the out-patient cystoscopy clinic at the General Infirmary at Leeds. After the patients had been weighed and given premedication with 0.65 mg. of atropine intramuscularly they were positioned and then given either 1 ml. (10 mg.) per 14 lb. (1.57 mg. per kg.) body weight of a 1% solution of methohexitone intravenously at a rate of 1 ml. every 3 seconds, or 1 ml. (25 mg.) per 14 lb. (3.93 mg. per kg.) of a 2.5% solution of thiopentone at a rate of 1 ml. every 2 seconds, supplementary doses of 2 to 3 ml. of the drugs being given if necessary. Anaesthesia was classified with reference to the occurrence of undesired movements during induction and instrumentation as: (1) no movement; (2) slight movement; (3) movement not interfering with instrumentation; and (4) inadequate control requiring inhalational anaesthesia. Inhalation of nitrous oxide-oxygen-halothane was necessary in only 6 cases. Patients were considered to be conscious when they responded to simple commands. The duration of anaesthesia, of instrumentation, and of the interval between "the end of instrumentation and recovery of consciousness" was noted, as were the pulse, systolic blood pressure, eyelash reflex, and any unusual phenomenon. Romberg's test was applied one hour after recovery.

Methohexitone was found to be three times more potent than thiopentone. In the majority of patients receiving this drug tremor and clonic movements of the hips, knees, and ankles developed which failed to respond to further doses. In the patients given thiopentone there was movement after surgical stimulus, which responded to further doses of the drug. No respiratory depression or airway difficulty was encountered with either drug and no significant change in pulse rate occurred, but in all the patients, given thiopentone there was a fall in the systolic blood pressure compared with only 56% of patients receiving methohexitone. A positive response to the Romberg test one hour after recovery was obtained in 77% of patients given thiopentone but in only 12% of those receiving methohexitone. The eyelash reflex was abolished in 77% of the thiopentone group and 0.23% of the methohexitone group. The authors consider that "if the eyelash reflex is used to assess the induction dose of methohexitone, unnecessarily large doses of the drug will be given".

Discussing their findings they state that the use of methohexitone was discontinued because of muscle movement. The incidence of hypotension was lower with methohexitone, but when a fall in systolic pressure did occur it was similar in extent to that seen in the patients given thiopentone. While the awakening time was the same for both drugs, the majority of patients receiving methohexitone were ready to go home after one hour, while those who received

thiopentone were not. A notable observation was that patients who had had thiopentone on previous visits to the clinic expressed a preference for methohexitone.

The authors conclude that methohexitone is preferable for the induction of anaesthesia in those cases in which rapid recovery "free from hangover" is desirable and hypotension is to be avoided.

Raymond Vale

1416. Methoxyflurane: a Clinical Evaluation of Its Effects, Based on Five Hundred Cases

R. E. KAVENEY and C. E. WASMUTH. *Cleveland Clinic Quarterly [Cleveland Clin. Quart.]* 29, 148-152, July, 1962.

The clinical value of methoxyflurane, a new, non-inflammable anaesthetic agent, has been assessed at the Cleveland Clinic Hospital in a series of 500 unselected patients aged 6 months to 74 years who were undergoing a variety of operative procedures. Anaesthesia was generally induced with thiopentone and "scoline" and, after intubation, methoxyflurane was administered by vaporization in a Heidbrink wick vaporizer in semi-closed or closed circuit or, in the case of 20 children, by an open-drop technique.

The blood pressure was found to be the most reliable guide to the depth of anaesthesia, a falling blood pressure indicating deepening anaesthesia. Respiratory depression was appreciable only during the deeper planes of anaesthesia. No abnormalities of cardiac rhythm were noted. Muscle relaxants were necessary for upper abdominal and, in some cases, for lower abdominal procedures; the dosage of tubocurarine had to be reduced to avoid profound falls in blood pressure. It is concluded that methoxyflurane produces excellent analgesia, but that induction and emergence from anaesthesia are relatively slow.

Mark Swerdlow

1417. Halothane versus Chloroform: the Dose Response Using the Isolated Rabbit Heart

M. ASHER and E. L. FREDERICKSON. *Anesthesia and Analgesia; Current Researches [Anesth. Analg. Curr. Res.]* 41, 429-434, July-Aug., 1962. 4 figs.; 20 refs.

We have shown that, in the isolated rabbit heart, halothane causes myocardial depression of no less severity than that seen with chloroform, and that the depression is predictable in a dose response fashion. In addition, the effect of halothane on the isolated heart rate has been shown to be unpredictable except at very high concentrations, when depression of the heart rate always occurs.—[Authors' summary.]

1418. Propiomazine; an Adjuvant for Obstetric Analgesia

R. D. GRIMALDI. *Anesthesia and Analgesia; Current Researches [Anesth. Analg. Curr. Res.]* 41, 487-496, July-Aug., 1962. 1 fig., 31 refs.

Propiomazine (1-(10-[2-dimethylaminopropyl] phenothiazine-2yl)-1-propanone) was given at the start of labour to 502 patients at the Metropolitan Medical Center, New York, 249 patients receiving 15 mg. of propiomazine, 50 mg. of pethidine, and 0.04 mg. of scopolamine (all intramuscularly), while the remaining 253 patients had the same dose of pethidine and scopolamine but double the dose of propiomazine. In both series the initial dose was repeated at intervals of 3 to 4 hours.

Good relief of pain was obtained in 200 (80%) of the patients receiving the lower dosage and in 220 (87%) of those given the higher dosage of propiomazine. However, it was

found that 30 mg. of propiomazine caused some increase in morbidity, and consequently the 15-mg. dose is recommended for general use. Blood-pressure measurements taken throughout labour and one and 2 hours post-partum showed that a rise in pressure of more than 10 mm. Hg occurred in 181 (36%) and a fall of 10 mm. Hg in 160 (31%) of the 502 patients; the blood-pressure changes were not sustained and were unrelated to the dose of propiomazine. The medication appeared to have no effect on the course of labour. The over-all incidence of nausea and vomiting was lower than in patients not receiving phenothiazine drugs. The Apgar score for 89% of the infants was 7 or more.

Mark Swerdlow

1419. Experimental and Clinical Experiences with a New Muscle Relaxant Ro 4-3816, Diallyl-nor-toxiferine. [In English]

I. LUND and J. STOVNER. *Acta anaesthesiologica Scandinavica [Acta anaesth. scand.]* 6, 85-97, 1962. 2 figs., 12 refs.

Ro 4-3816 (diallyl-nor-toxiferine) is a new muscle relaxant of the non-depolarizing type. This derivative of the calabash alkaloid "toxiferine C" has been tested experimentally and clinically and compared with D-tubocurarine. It has been given a trial in a total of 400 patients.

The new relaxant appears to be approximately 1.5 times more potent than D-tubocurarine when tested on the grip strength of conscious human volunteers and on the RMV [respiratory minute volume] of anaesthetized patients. Approximately the same dose relationship was found when Ro 4-3816 was used clinically to facilitate tracheal intubation and to produce muscular relaxation during laparotomy. The onset and duration of action of this compound were found to be similar to those of D-tubocurarine for equipotent doses. Supplementary doses of Ro 4-3816 during the second and third hours of anaesthesia, respectively, needed to be only one-sixth to one-ninth of the doses used during the first hour. The same was found for D-tubocurarine. No difference could be demonstrated in the cumulative action of the two drugs.

"Prostigmin" [neostigmine] 0.5 to 1 mg. or "tensilon" [edrophonium] 10 mg. always produced a rapid and complete reversal of residual curarization after Ro 4-3816, while 1 to 2 mg. prostigmin was needed when D-tubocurarine was used.

Pulse and blood pressure were not affected by Ro 4-3816, and ECG [electrocardiogram] changes were absent in the 10 patients observed. No signs of histamine liberation or any other untoward effects were observed.—[Authors' summary.]

1420. Effect of Succinylcholine on Uterine Motility. [In English]

N. WIGVIST and A. WÄHLIN. *Acta anaesthesiologica Scandinavica [Acta anaesth. scand.]* 6, 71-75, 1962. 13 refs.

Clinical observations during certain obstetrical operations—for example, manual removal of the retained placenta—performed under general anaesthesia suggested a possible relaxation of the uterus after the injection of succinylcholine. In this paper from Karolinska Sjukhuset and Karolinska Institutet, Stockholm, a study is reported of the effect of succinylcholine on the uterus in pregnant women and in animals. No noticeable change in the motility could be demonstrated.—[From the authors' summary.]

Radiology

1421. **Investigation of the Protective Value of Laminated Rubber Sheets in X-ray Installations.** (Исследование защитной слонстой резины для рентгенозащитных устройств)

A. N. KRONGAUZ, S. I. VORONA, and E. I. UNANOV. *Вестник Рентгенологии и Радиологии* [Vestn. Rentgenol. Radiol.] 37, 60-62, May-June, 1962, 2 figs.

The protective value of laminated rubber sheets was found to exceed the sum total of the protective values of the individual layers making up the sheets. The sheets were composed of two layers of protective rubber. One layer consisted of lead rubber, while the second layer owed its protective properties to the presence of barium sulphate. In some instances the protective value of the laminated sheet exceeded the expected value by as much as 25%. The additive protective effect of the lamination was most marked at 80 kV. and least marked at 120 kV. A. Orley

1422. **The Genetic Effect of Radiotherapy in Skin Diseases.** (Zur Frage der Strahlenbelastung der Bevölkerung durch die dermatologische Röntgentherapie) G. WAGNER. *Strahlentherapie* [Strahlentherapie] 118, 122-144, May, 1962. 19 figs., 19 refs.

This is a report of experience gained at the University of Kiel between 1953 and 1960, when 1,712 radiation treatments for dermatological conditions were given to 1,510 patients. Information concerning age, sex, diagnosis, body sites, radiation qualities, repetition of treatment, and size of field is given in charts and tables. The following are some of the principal points which emerged from the study. In the first decade of life females outnumbered males, chiefly because of the number of cases treated for angioma, but radiation treatment of this condition has been practically given up since 1958. The percentage of patients past reproductive age (taken as 45) was 61-65% of the females and 56% of the males. Since 1954 the average age of patients treated by radiation has increased, while the total number has decreased, largely because of the newer corticosteroid therapy available for eczema. Only 5.9% of the patients, of whom 24% were under 40 years of age, received treatment in the ano-genito-inguinal region. If trunk and thigh are included, only one-third of all treatments were of genetic significance. Since 1954 the quality of radiation used has been mainly that of Grenz rays—[that is, softer rays than were used in the comparable series of the Adrian report]. Repeated courses of treatment were given mainly in cases of mycosis fungoides. Fields of less than 10 sq. cm. were used in 9.9% of cases and fields exceeding 1,000 sq. cm. in 15.2%.

Some interesting comparisons are drawn with data given by Welton and Greenberg (*Arch. Derm.*, 1961, 83, 355) for the U.S.A. For example, in the U.S.A. 25% of all dermatological patients received radiation treatment, whereas in Kiel only 6.4% of such patients were so treated. In the U.S.A. irradiation of patients under 45 years of age was 7 times as frequent as in Kiel. There are also considerable differences in the type of case most often treated. The evidence available in the literature suggests that the genetically

significant dose from external radiation therapy is 2.5 mr. per person per year, which is about the same as that due to radiation from luminous watch dials. J. Walter

RADIODIAGNOSIS

1423. **Selective Transseptal Angiocardiography of the Left Side of the Heart**

J. S. MACDONALD and B. L. MILLER. *Clinical Radiology* [Clin. Radiol.] 13, 195-200, July, 1962. 7 figs., 25 refs.

For clear demonstration of the cardiac chambers the contrast medium must be restricted to, and so far as possible fill out, the chambers of interest. There has been a continuing search for safe and accurate methods of placing catheters which are strong enough and have a wide enough lumen to achieve this aim. Interest in the application of selective angiocardiography to the left side of the heart is recent and has been stimulated by the widening range of cardiac surgery since the introduction of hypothermia and cardiac by-pass techniques.

At St. Thomas's Hospital, London, left heart catheterization by the transseptal left atrial puncture technique was carried out on 65 occasions and 10 left-sided angiocardiograms were obtained. The catheter used was a large (P.E. 205) Ödman catheter with an outer diameter of 2.85 mm. and an inner diameter of 1.5 mm. A thin-walled, 17-gauge, stainless steel Ross needle 61 cm. long was used. The catheter was introduced by cutting down on the right long saphenous vein. (It may also be introduced by percutaneous puncture of the right femoral vein.) If catheterization is performed via the left leg it is not easy to contact the septum with the needle tip in a suitable position for puncture. With the catheter tip in the right atrium the Ross needle was passed during continuous fluoroscopy. When pressure tracings had confirmed that the needle tip was in the left atrium, the catheter was slid along the needle, and when the catheter itself was in the left atrium the needle was withdrawn completely. The pre-set curve in the catheter enabled it to be passed through the mitral valve into the left ventricle. The over-all success rate was 83%, but 91% in the second half of the series. Once the septum had been punctured, there were no instances of failure to place the catheter tip in the desired position. The technique caused no deaths and no significant morbidity. Of the 10 angiocardiograms only one was a failure, and this was due to a mechanical breakdown in a serial changer. The contrast medium used was 85% "hypaque" given in a maximum dose of 1 ml. per kg. body weight, and no repeat injections were needed. The injection was made at a pressure of 75 lb. per sq. in. (5.27 kg. per sq. cm.). A biplane serial changer capable of 6 films per second in each plane was used. Maximum kV. was 130 and exposures did not exceed 20 msec. A short exposure is necessary to show valvular detail. The films were obtained in the true antero-posterior and lateral planes. The catheter was manipulated under local anaesthesia, except in young children. A general anaesthetic was given

for angiocardiology. This technique is considered suitable only for a team thoroughly familiar with cardiac catheterization.

John H. L. Conway-Hughes

1424. The Hilum in Pulmonary Venous Hypertension

J. P. LAVENDER and J. DOPPMAN. *British Journal of Radiology* [Brit. J. Radiol.] 35, 303-313, May, 1962. 11 figs., 27 refs.

In this paper from Hammersmith Hospital and the Postgraduate Medical School of London, an analysis is presented of the components of the normal right hilum and the changes occurring in left ventricular failure and mitral valvular disease.

The hilum was studied on plain radiographs and tomograms in 48 healthy subjects, 45 patients with left ventricular failure, and 33 patients with mitral valvular disease. The normal right hilum consists of a smaller upper part composed mainly of descending upper-lobe veins; the superior pulmonary vein crosses the descending pulmonary artery, the angle between the two forming a useful point of division of the hilum into upper and lower parts. The lower part is dominated by the descending pulmonary artery. There is thus normally a concave lateral hilar border and the upper part of the hilum will reflect venous changes, whereas the lower will be influenced by arterial changes.

In mitral disease there is a correlation between the severity of pulmonary arterial hypertension and the size of the pulmonary artery so that varying degrees of lower hilar enlargement are seen, but the main feature is the increase in upper-lobe vein size causing preponderance of the upper hilum with a straight or convex lateral hilar border. The lower margin of the superior pulmonary vein is better defined than in the normal hilum and crosses the descending pulmonary artery lower and more laterally.

In over 50% of cases of left ventricular failure, especially those of acute failure with pulmonary oedema, there is pulmonary arterial enlargement, suggesting pulmonary arterial hypertension, but the enlargement never reaches the degree seen in patients with mitral valve disease with pulmonary hypertension. The pulmonary veins are also enlarged and tend to fill in the angle between the upper and lower parts, producing a straight or convex lateral hilar border.

Except in severe mitral disease with pulmonary arterial hypertension, the hilar changes in mitral disease cannot be distinguished from those in left ventricular failure; in both the appearances are due mainly to pulmonary venous hypertension, which causes the two important signs: (1) altered lateral hilar contour, and (2) a prominent clearly defined lower margin to the superior pulmonary vein.

Michael C. Winter

1425. A Comparison of Intravenous Urography, Urine

brated in terms of the radiographic densities of known concentrations of sodium diatrizoate. Since the first report 415 intravenous pyelograms recorded at the Medical College of Georgia, Augusta, have been reviewed and compared with the results of urine radiography and other renal function tests on the same patients. Correction of the results of urine radiography was made for residual urine after micturition, and renal function was assessed from the pyelograms by a method which involved assigning a "point value" to the visual density of the image of each kidney on the 10- and 20-minute films, adding these points together, and finally adding a value derived by means of a formula from the density value of the bladder at 20 minutes and the volume of the specimen voided at 30 minutes (corrected for retention).

From their study of this series of cases the authors conclude that urine radiography is a sensitive test of renal function, the results of which correlate well with those obtained by visual estimation from the intravenous pyelogram (which they regard as another reliable test). They consider that the blood urea nitrogen level depends on too many extrarenal factors for it to be of much use as a test of renal function and that the creatinine clearance test is also inferior to urine radiography. The phenolsulphonphthalein excretion test provides the closest correlation with urine radiography and is probably the best guide in determining whether to perform intravenous or retrograde pyelography.

D. E. Fletcher

1426. Angiography of the Renal Areas, Including a Comparative Study of Renal Arterial Stenoses in Patients With and Without Hypertension

W. R. EYLER, M. D. CLARK, J. E. GARMAN, R. L. RIAN, and D. E. MEININGER. *Radiology* [Radiology] 78, 879-892, June, 1962. 11 figs., 12 refs.

Stenosis of the renal artery may be associated with a normal blood pressure. To investigate the effects of renal arterial disease on the blood pressure renal angiograms from 500 patients were reviewed at the Henry Ford Hospital, Detroit, together with their clinical records, excretory urograms and, where available, isotope renograms, surgical findings, and pathological reports. The blood pressure of 304 of the patients was normal, while the remaining 196 had a diastolic pressure persistently above 90 mm. Hg. All types of renal arterial abnormality were found in both groups, but were more frequent in the hypertensives. Severe stenosis narrowing the lumen to less than 2 mm. was present in 10 hypertensives and in 8 patients with normal blood pressure. One or more plaques were present in the renal arteries of 77 hypertensives and 66 normotensives, associated in about half of each group with post-stenotic dilatation.

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